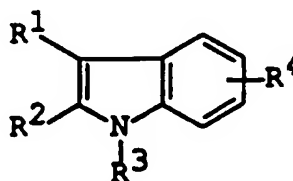




INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07D 209/12, A61K 31/40, C07D 401/12, 403/12, 409/06, 405/06, 401/06, 403/04, 417/06, 209/42, 209/30, 209/88, 209/70		A1	(11) International Publication Number: WO 96/32379
			(43) International Publication Date: 17 October 1996 (17.10.96)
(21) International Application Number: PCT/JP96/00892		Tsukuba-shi, Ibaraki 305 (JP). NAGASHIMA, Akira [JP/JP]; 4-22-2-204, Matsushiro, Tsukuba-shi, Ibaraki 305 (JP). SOGABE, Keizo [JP/JP]; 1-4-8, Ottominami, Tsuchiura-shi, Ibaraki 300 (JP). TAMURA, Kouichi [JP/JP]; 1-7-3, Nishimaya, Kita-ku, Kobe-shi, Hyogo 651-13 (JP). KOBAYASHI, Masakazu [JP/JP]; 23-4, Hanayashikimatsugaoka, Takarazuka-shi, Hyogo 665 (JP). (74) Agent: SEKI, Hideo; Fujisawa Pharmaceutical Co., Ltd., Osaka Factory, 1-6, Kashima 2-chome, Yodogawa-ku, Osaka-shi, Osaka 532 (JP). (81) Designated States: AU, CA, CN, HU, JP, KR, MX, NO, NZ, US, Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).	
(22) International Filing Date: 2 April 1996 (02.04.96)			
(30) Priority Data: 9507432.4 10 April 1995 (10.04.95) GB 9512560.5 21 June 1995 (21.06.95) GB 9516136.0 7 August 1995 (07.08.95) GB PN 8294 27 February 1996 (27.02.96) AU			
(71) Applicant (for all designated States except US): FUJISAWA PHARMACEUTICAL CO., LTD. [JP/JP]; 4-7, Doshomachi 3-chome, Chuo-ku, Osaka-shi, Osaka 541 (JP).			
(72) Inventors; and		Published With international search report.	
(75) Inventors/Applicants (for US only): OKU, Tetsuo [JP/JP]; 8-2, Modorigaoka, Tsukuba-shi, Ibaraki 305 (JP). SAWADA, Kozo [JP/JP]; 1-4-3-602-301, Azuma, Tsukuba-shi, Ibaraki 305 (JP). KURODA, Akio [JP/JP]; 3-18-2-203, Matsushiro, Tsukuba-shi, Ibaraki 305 (JP). OHNE, Kazuhiko [JP/JP]; 2-25-10, Matsushiro, Tsukuba-shi, Ibaraki 305 (JP). NOMOTO, Atsushi [JP/JP]; 1-17-22, Arakawaokinishi, Tsuchiura-shi, Ibaraki 300-11 (JP). HOSOGAI, Naomi [JP/JP]; 2-9-11-409, Amakubo, Tsukuba-shi, Ibaraki 305 (JP). NAKAJIMA, Yoshimitsu [JP/JP]; 168, Nishihirotsuka,			
(54) Title: INDOLE DERIVATIVES AS cGMP-PDE INHIBITORS			
(57) Abstract			

This invention relates to new indole derivatives of formula (I), wherein R¹ is hydrogen, halogen, nitro, carboxy, protected carboxy, acyl, etc., R² is hydrogen, halogen, lower alkenyl, acyl, etc., R³ is lower alkenyl or lower alkyl, both of which are optionally substituted with aryl optionally substituted with one or more substituent(s) selected from the group consisting of halogen, aryl, lower alkoxy, etc., and R⁴ is carboxy, protected carboxy, acyl, etc., in addition to their significances above, R¹ and R², together with the carbon atoms to which they are attached, represent a 4- to 7-membered carboxylic ring optionally substituted with oxo, or its pharmaceutically acceptable salt, which is useful as a medicament; and to new use of cyclic nucleotide-PDE inhibitors.



(I)

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	GB	United Kingdom	MW	Malawi
AT	Austria	GE	Georgia	MX	Mexico
AU	Australia	GN	Guinea	NE	Niger
BB	Barbados	GR	Greece	NL	Netherlands
BE	Belgium	HU	Hungary	NO	Norway
BF	Burkina Faso	IE	Ireland	NZ	New Zealand
BG	Bulgaria	IT	Italy	PL	Poland
BJ	Benin	JP	Japan	PT	Portugal
BR	Brazil	KE	Kenya	RO	Romania
BY	Belarus	KG	Kyrgyzstan	RU	Russian Federation
CA	Canada	KP	Democratic People's Republic of Korea	SD	Sudan
CF	Central African Republic	KR	Republic of Korea	SE	Sweden
CG	Congo	KZ	Kazakhstan	SG	Singapore
CH	Switzerland	LJ	Liechtenstein	SI	Slovenia
CI	Côte d'Ivoire	LK	Sri Lanka	SK	Slovakia
CM	Cameroon	LR	Liberia	SN	Senegal
CN	China	LT	Lithuania	SZ	Swaziland
CS	Czechoslovakia	LU	Luxembourg	TD	Chad
CZ	Czech Republic	LV	Latvia	TG	Togo
DE	Germany	MC	Monaco	TJ	Tajikistan
DK	Denmark	MD	Republic of Moldova	TT	Trinidad and Tobago
EE	Estonia	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	UG	Uganda
FI	Finland	MN	Mongolia	US	United States of America
FR	France	MR	Mauritania	UZ	Uzbekistan
GA	Gabon			VN	Viet Nam

- 1 -

DESCRIPTION

INDOLE DERIVATIVES AS cGMP-PDE INHIBITORS

5 This invention relates to novel compounds having pharmacological activity, to a process for their production and to a pharmaceutical composition containing the same.

 More particularly, it relates to novel indole compounds, which have pharmaceutical activity such as inhibiting
10 activity of cyclic guanosine 3',5'-monophosphate phosphodiesterase (hereinafter described as cGMP-PDE), to a process for their production, to a pharmaceutical composition containing the same and to a use thereof.

 Accordingly, one object of this invention is to provide
15 the novel indole compounds, which have an inhibiting activity of cGMP-PDE.

 Another object of this invention is to provide a process for production of the indole compounds.

 A further object of this invention is to provide a
20 pharmaceutical composition containing, as active ingredients, the indole compounds.

 Still further object of this invention is to provide a
25 use of the indole compounds for treating or preventing various diseases.

 Further, this invention also relates to a new use of inhibitors of cyclic nucleotide phosphodiesterases.
(hereinafter described as cyclic nucleotide-PDEs)

 In more detail, this invention relates to a new use of
30 cyclic nucleotide-PDEs inhibitors for preventing or treating glomerular diseases, tubulo-interstitial diseases or renal failure, or diabetic complications.

 Accordingly, this invention provides a new use of cyclic
35 nucleotide-PDE inhibitors for preventing or treating glomerular diseases, tubulo-interstitial diseases or renal

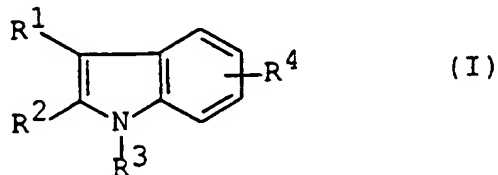
- 2 -

failure, or diabetic complications.

Further, this invention provides an agent and a pharmaceutical composition for preventing or treating glomerular diseases, tubulo-interstitial diseases or renal failure, or diabetic complications, which comprises cyclic nucleotide-PDE inhibitors.

Still further, this invention provides a method for preventing or treating glomerular diseases, tubulo-interstitial diseases or renal failure, or diabetic complications, which comprises administering cyclic nucleotide-PDE inhibitors.

The new indole compounds of this invention can be represented by the following general formula :



wherein

R¹ is hydrogen, halogen, nitro, carboxy, protected carboxy, acyl, cyano, hydroxyimino(lower)alkyl, lower alkenyl optionally substituted with oxo, or lower alkyl optionally substituted with protected carboxy, carboxy or hydroxy;

R² is hydrogen, halogen, lower alkenyl, acyl, or lower alkyl optionally substituted with protected carboxy, carboxy, lower alkoxy or hydroxy;

R³ is lower alkenyl or lower alkyl, both of which are optionally substituted with one or more substituent(s) selected from the group consisting of

(1) oxo,

- 3 -

- (2) aryl optionally substituted with one or more substituent(s) selected from the group consisting of halogen, aryl, lower alkoxy, lower alkylenedioxy, cyano, nitro, carboxy, protected carboxy, acyl, and amino optionally substituted with acyl or protected carboxy, and
- (3) a heterocyclic group optionally substituted with halogen; and

R⁴ is carboxy, protected carboxy, acyl, cyano, halogen, a heterocyclic group, amino optionally substituted with acyl or protected carboxy, or lower alkyl optionally substituted with protected carboxy, carboxy or acyl; in addition to their significances above,

R¹ and R², together with the carbon atoms to which they are attached, represent a 4- to 7-membered carbocyclic ring optionally substituted with oxo, or its pharmaceutically acceptable salt.

The compounds of formula (I) may contain one or more asymmetric centers and thus they can exist as enantiomers or diastereoisomers. Furthermore certain compounds of formula (I) which contain alkenyl groups may exist as cis- or trans-isomers. In each instance, the invention includes both mixtures and separate individual isomers.

The compounds of formula (I) may also exist in tautomeric forms and the invention includes both mixtures and separate individual tautomers.

The compound of the formula (I) and its salt can be in the form of a solvate, which is included within the scope of the present invention. The solvate preferably include a hydrate and an ethanolate.

Also included in the scope of invention are radiolabelled derivatives of compounds of formula (I) which are suitable for biological studies.

- 4 -

A preferred group of compounds of formula (I) is that wherein

R¹ is cyano, acyl, or lower alkyl optionally substituted with hydroxy;

R² is hydrogen, acyl, lower alkenyl, or lower alkyl optionally substituted with lower alkoxy or hydroxy;

R³ is methyl substituted with aryl or a heterocyclic group, wherein aryl is optionally substituted with one or more substituent(s) selected from the group consisting of halogen, lower alkylenedioxy, protected carboxy and carboxy; and

R⁴ is acyl, cyano, or a heterocyclic group;

in addition to their significances above,

R¹ and R², together with the carbon atoms to which they are attached, represent a 4- to 7-membered carbocyclic ring optionally substituted with oxo.

A more preferred group of compounds of formula (I) is that wherein

R¹ is lower alkyl, or lower alkanoyl optionally substituted with hydroxy, lower alkoxy or aryl;

R² is hydrogen, lower alkenyl, or lower alkyl optionally substituted with lower alkoxy;

R³ is benzyl optionally substituted with one or more substituent(s) selected from the group consisting of halogen and lower alkylenedioxy; and

R⁴ is acyl, cyano, or a heterocyclic group.

A particularly preferred group of compounds of formula (I) is that wherein

R¹ is lower alkyl, or lower alkanoyl optionally substituted with hydroxy, lower alkoxy or aryl;

R² is hydrogen, lower alkenyl, or lower alkyl optionally substituted with lower alkoxy;

R³ is benzyl optionally substituted with one or more

- 5 -

substituent(s) selected from the group consisting of halogen and lower alkylenedioxy;

R^4 is $-\text{CON} \begin{matrix} \nearrow R^5 \\ \searrow R^6 \end{matrix}$;

R^5 is hydrogen or lower alkyl, and

R^6 is hydrogen, hydroxy, lower alkoxy, arylsulfonyl, a heterocyclic group, or lower alkyl optionally substituted with lower cycloalkyl or a heterocyclic group;

in addition to their significances above,

R^5 and R^6 , together with the nitrogen atom to which they are attached, may represent a heterocyclic group.

An especially preferred group of compounds of formula

(I) is that wherein

R^1 is lower alkanoyl optionally substituted with alkoxy,

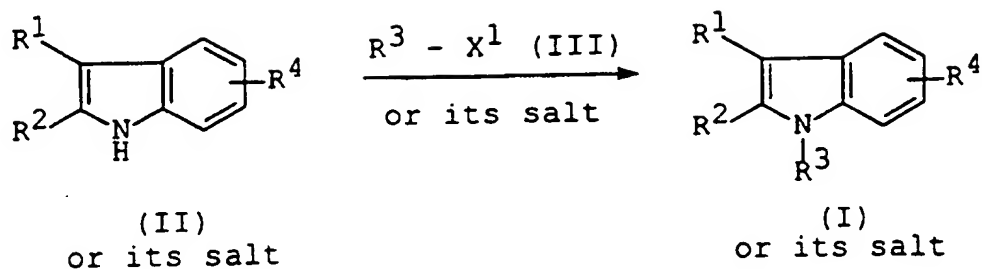
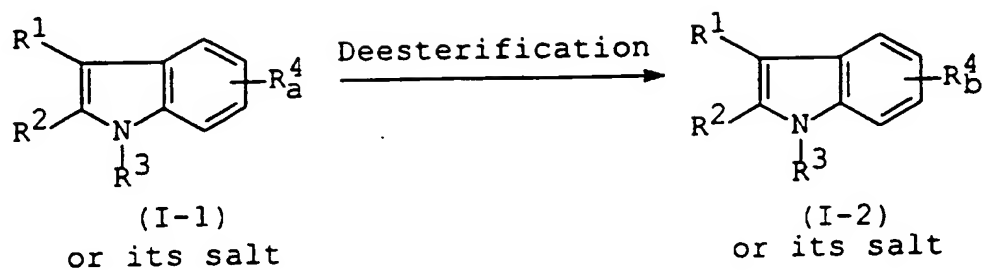
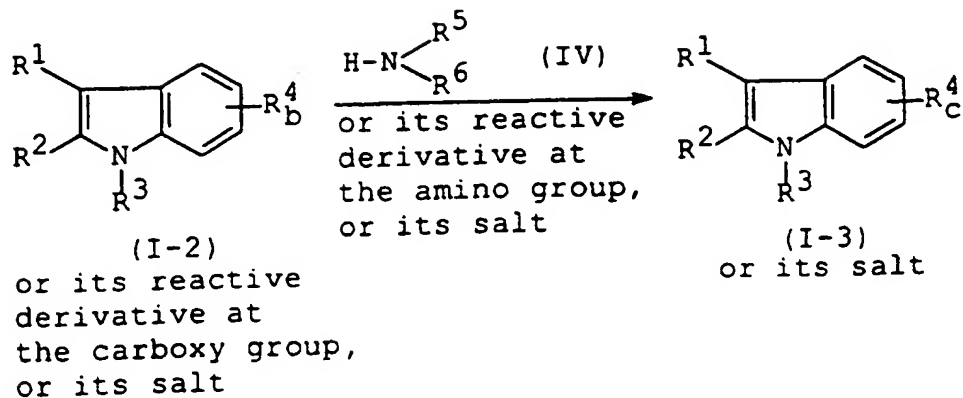
R^2 is lower alkyl,

R^3 is benzyl optionally substituted with one or more substituent(s) selected from the group consisting of halogen and lower alkylenedioxy, and

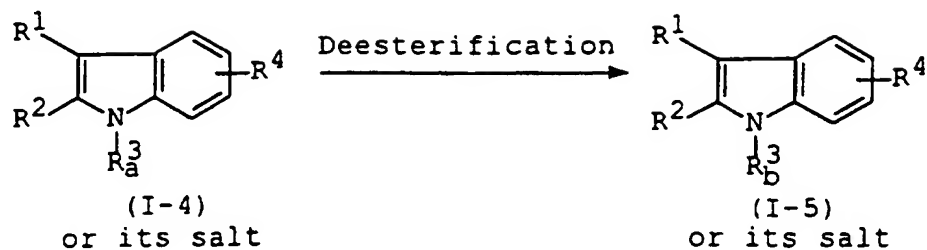
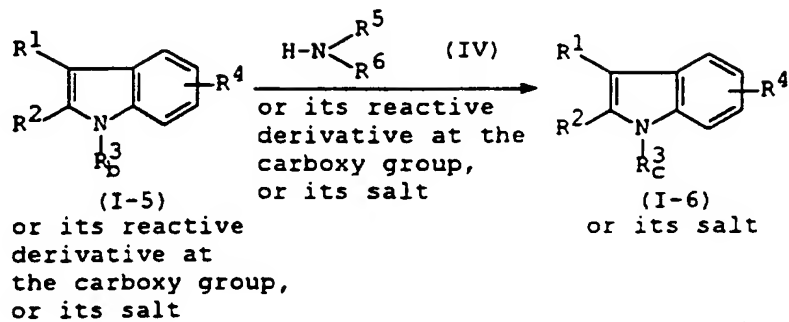
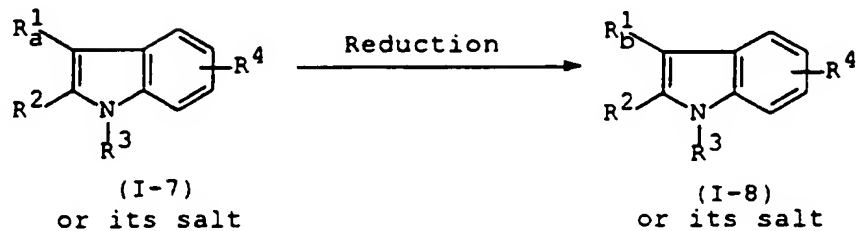
R^4 is carbamoyl.

According to this invention, the object compounds (I) or its salt can be prepared by the following processes.

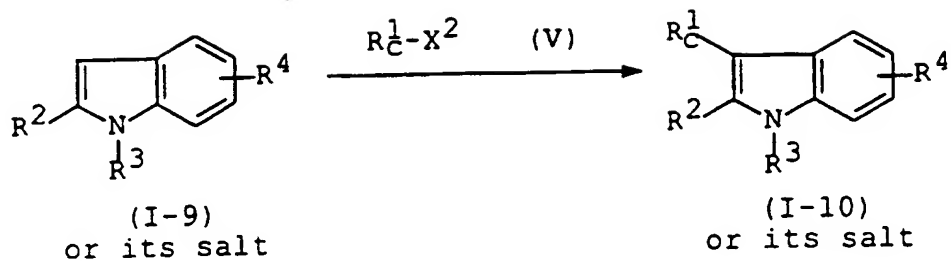
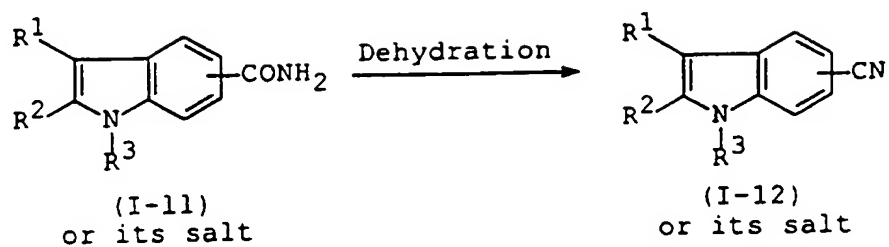
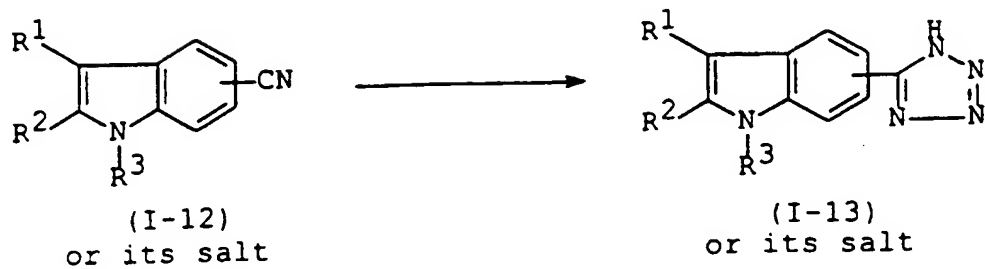
- 6 -

Process 1Process 2Process 3

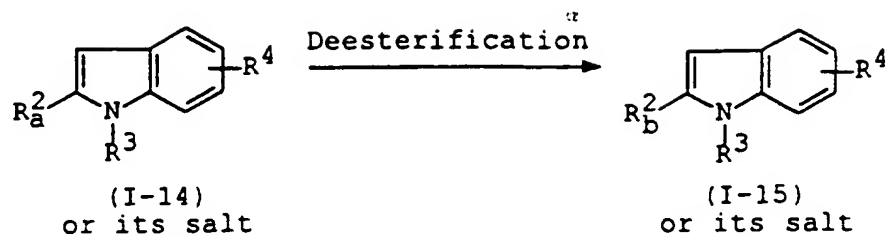
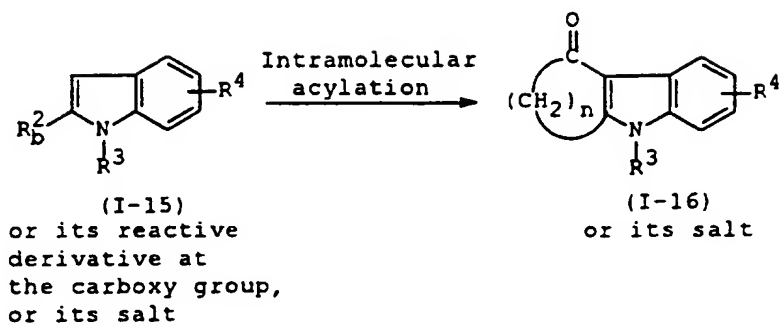
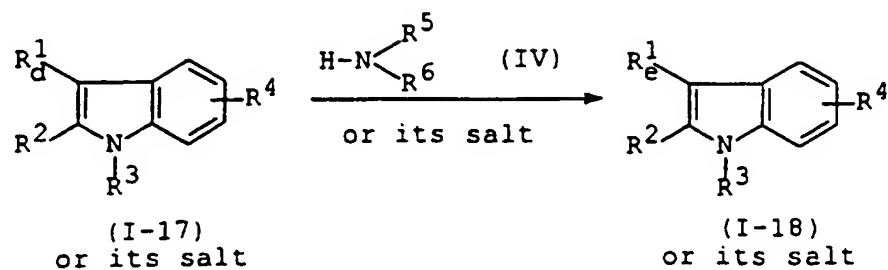
- 7 -

Process 4Process 5Process 6

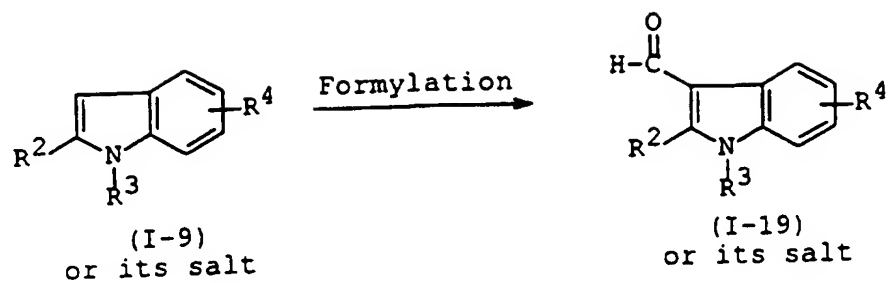
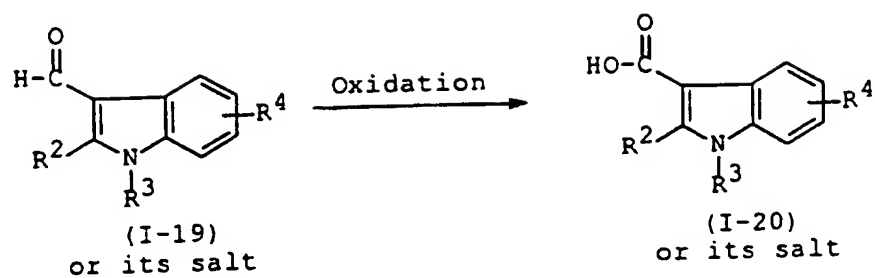
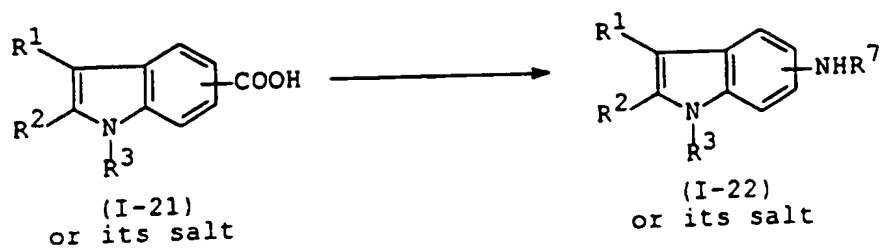
- 8 -

Process 7Process 8Process 9

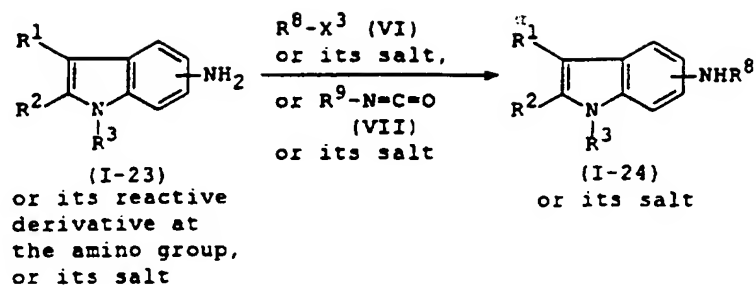
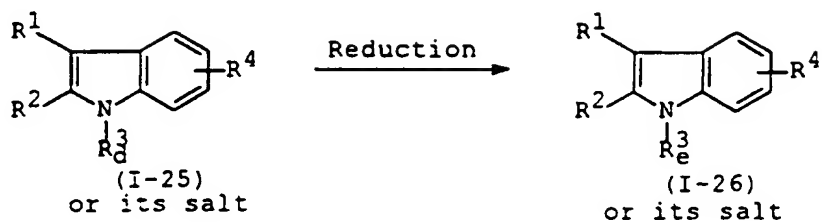
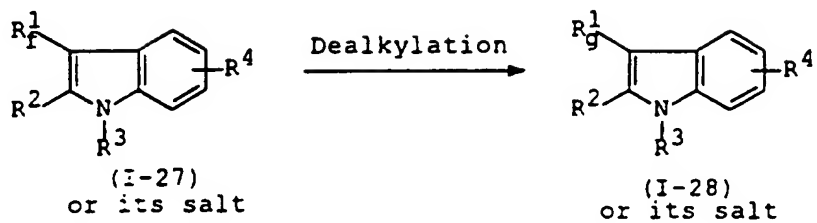
- 9 -

Process 10Process 11Process 12

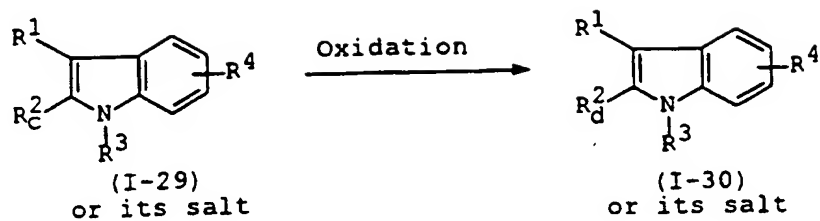
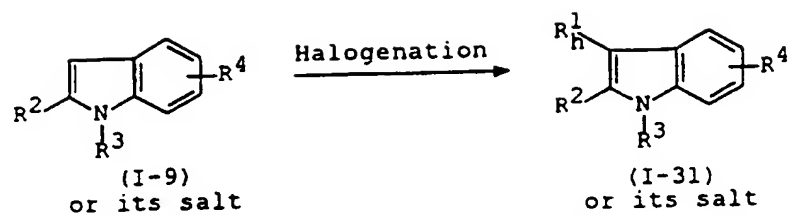
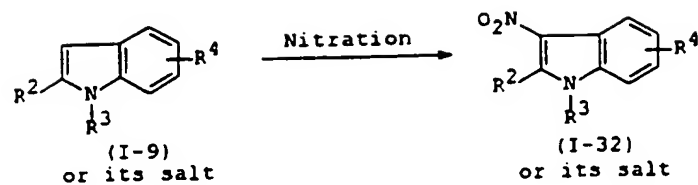
- 10 -

Process 13Process 14Process 15

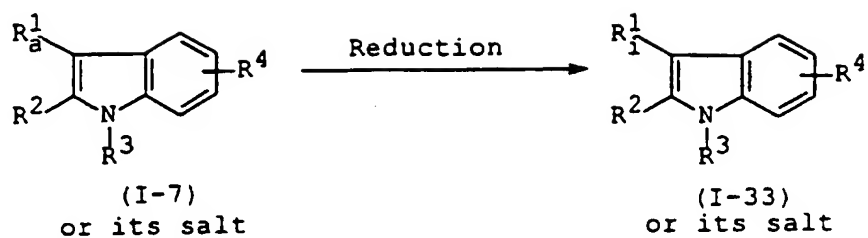
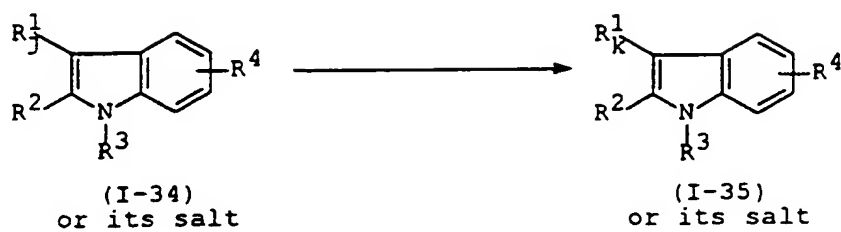
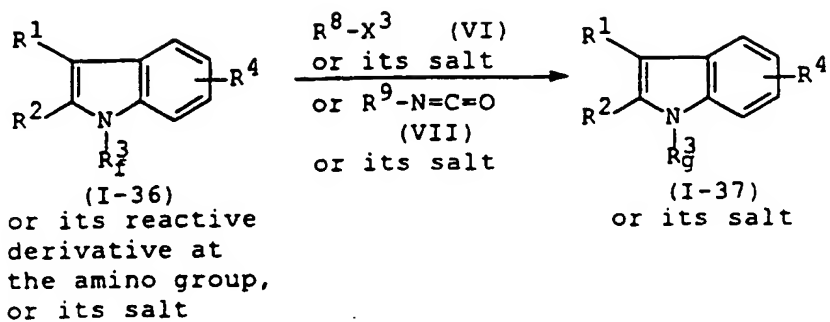
- 11 -

Process 16Process 17Process 18

- 12 -

Process 19Process 20Process 21

- 13 -

Process 22Process 23Process 24

- 14 -

wherein

R^1 to R^6 are each as defined above,

R_a^1 is lower alkanoyl optionally substituted with protected carboxy or carboxy,

R_b^1 is lower alkyl optionally substituted with protected carboxy or carboxy,

R_c^1 is lower alkenoyl, aroyl, or lower alkanoyl optionally substituted with protected carboxy, carboxy or aryl,

R_d^1 is chloroacetyl,

R_e^1 is $-\text{COCH}_2\text{N} \begin{smallmatrix} \nearrow R^5 \\ \searrow R^6 \end{smallmatrix}$,

R_f^1 is lower alkanoyl substituted with lower alkoxy,

R_g^1 is lower alkanoyl substituted with hydroxy,

R_h^1 is halogen,

R_i^1 is lower alkyl optionally substituted with protected carboxy or carboxy,

R_j^1 is lower alkanoyl,

R_k^1 is hydroxyimino(lower)alkyl,

R_a^2 is lower alkyl substituted with protected carboxy,

R_b^2 is lower alkyl substituted with carboxy,

R_c^2 is 1-hydroxy(lower)alkyl,

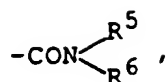
R_d^2 is lower alkanoyl,

R_a^3 is lower alkenyl or lower alkyl, both of which are optionally substituted with oxo and both of which are substituted with aryl which is substituted with protected carboxy,

R_b^3 is lower alkenyl or lower alkyl, both of which are optionally substituted with oxo and both of which are substituted with aryl which is substituted with carboxy,

R_c^3 is lower alkenyl or lower alkyl, both of which are optionally substituted with oxo and both of which are substituted with aryl which is substituted with

- 15 -



R_d^3 is lower alkenyl or lower alkyl, both of which are optionally substituted with oxo and both of which are substituted with aryl which is substituted with nitro,

R_e^3 is lower alkenyl or lower alkyl, both of which are optionally substituted with oxo and both of which are substituted with aryl which is substituted with amino,

R_f^3 is lower alkenyl or lower alkyl, both of which are optionally substituted with oxo and both of which are substituted with aryl which is substituted with amino,

R_g^3 is lower alkenyl or lower alkyl, both of which are optionally substituted with oxo and both of which are substituted with aryl which is substituted with amino substituted with acyl,

R_a^4 is protected carboxy or lower alkyl substituted with protected carboxy,

R_b^4 is carboxy or lower alkyl substituted with carboxy,

R_c^4 is $-\text{CON} \begin{array}{l} \nearrow \text{R}^5 \\ \searrow \text{R}^6 \end{array}$ or lower alkyl substituted with $-\text{CON} \begin{array}{l} \nearrow \text{R}^5 \\ \searrow \text{R}^6 \end{array} ,$

R^7 is hydrogen, protected carboxy, or $-\text{CON} \begin{array}{l} \nearrow \text{R}^5 \\ \searrow \text{R}^6 \end{array} ,$

R^8 is acyl,

R^9 is lower alkyl,

X^1 is leaving group,

X^2 and X^3 are each as the same as X^1 , and

n is 1, 2, 3 or 4.

In the above and subsequent description of the present specification, suitable examples of the various definitions to be included within the scope of the invention are explained in detail in the following.

- 16 -

The term "lower" is intended to mean a group having 1 to 6 carbon atom(s), unless otherwise provided.

Suitable "lower alkyl" and lower alkyl moiety in the terms "lower alkoxy" and "hydroxyimino(lower)alkyl", may be a
5 straight or branched C₁-C₆ alkyl such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, hexyl or the like, in which preferable one is C₁-C₄ lower alkyl such as methyl, ethyl, propyl, butyl, isobutyl or tert-butyl.

Suitable "lower alkenyl" may be a straight or branched
10 C₂-C₆ alkenyl such as ethenyl, propenyl (i.e. allyl or 1-propenyl), butenyl, isobutenyl, or the like.

Suitable "lower cycloalkyl" may include one having 3 to 6 carbon atoms, for example, cyclopropyl, cyclobutyl, cyclopentyl, or the like.

Suitable "aryl" and aryl moiety in the term of
15 "arylsulfonyl", "aroyl" and "ar(lower)alkanoyl" may include phenyl, naphthyl, tolyl, mesityl, xylyl, or the like.

Suitable "halogen" may be fluoro, chloro, bromo or iodo.

Suitable "lower alkylenedioxy" may include
20 methylenedioxy, ethylenedioxy, or the like.

Suitable "protected carboxy" may be a pharmaceutically acceptable and a common protected carboxy, such as an esterified carboxy, or the like, and concrete examples of the ester moiety in said esterified carboxy may be lower alkyl
25 optionally substituted with aryl (e.g. methyl, ethyl, propyl, tert-butyl, benzyl, and so on).

Suitable "heterocyclic group" may be one containing at least one hetero atom selected from nitrogen, sulfur and oxygen atom, and may include saturated or unsaturated,
30 monocyclic or polycyclic heterocyclic group such as (1) unsaturated 3 to 7-membered, preferably 5 or 6-membered heteromonocyclic group containing 1 to 4 nitrogen atoms, for example, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazolyl [e.g.
35 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl,

- 17 -

etc.], tetrazolyl [e.g. 1H-tetrazolyl, 2H-tetrazolyl, etc.], etc.;

(2) saturated 3 to 7-membered, preferably 5 or 6-membered heteromonocyclic group containing 1 to 4 nitrogen atoms [e.g. pyrrolidinyl, imidazolidinyl, piperidino, piperazinyl, etc.];

(3) unsaturated condensed heterocyclic group containing 1 to 5 nitrogen atoms, for example, indolyl, isoindolyl, indoliziny, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, tetrazolopyridazinyl [e.g.

tetrazolo[1,5-b]pyridazinyl, etc.], etc.;

(4) unsaturated 3 to 7-membered, preferably 5 or 6-membered heteromonocyclic group containing an oxygen atom, for example, pyranyl, furyl, etc.;

(5) unsaturated, 3 to 7-membered, preferably 5 or 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms, for example, thienyl, etc.;

(6) unsaturated 3 to 7-membered, preferably 5 or 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, for example, oxazolyl, isoxazolyl, oxadiazolyl [e.g. 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, etc.], etc.;

(7) saturated 3 to 7-membered, preferably 5 or 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms [e.g. morpholinyl, etc.];

(8) unsaturated condensed heterocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms [e.g. benzoxazolyl, benzoxadiazolyl, etc.];

(9) unsaturated 3 to 7-membered, preferably 5 or 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms, for example, thiazolyl, thiadiazolyl [e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, etc.], etc.

(10) saturated 3 to 7-membered, preferably 5 or 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms [e.g., thiazolidinyl, etc.];

- 18 -

(11) unsaturated condensed heterocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms [e.g., benzothiazolyl, benzothiadiazolyl, etc.];

5 (12) unsaturated condensed heterocyclic group containing 1 to 2 sulfur atoms or 1 to 2 oxygen atoms [e.g., benzothiophen, benzofuran, etc.]; or the like.

"Heterocyclic group" defined above may be substituted with suitable substituent(s) such as lower alkyl, hydroxy, halogen, a heterocyclic group, or the like (e.g., 3-
10 hydroxypyrrolidine, 4-methylpiperadine, 4-hydroxypiperidine, 1-methylimidazole, 4-(pyrimidin-2-yl)piperazin, and so on).

Suitable "acyl" may be aliphatic acyl, aromatic acyl or aliphatic acyl optionally substituted aryl, which are derived
15 from carboxylic acid or carbamic acid.

The aliphatic acyl may include

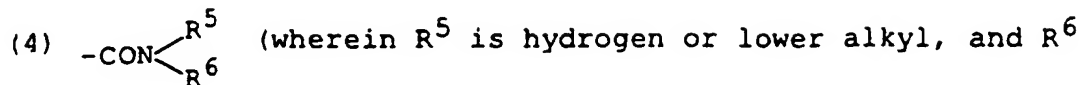
(1) lower alkanoyl optionally substituted with one or more suitable substituent(s) such as hydroxy, lower alkoxy, carboxy, protected carboxy, halogen, lower alkylthio,
20 heterocyclicthio, oxo, cyclo(lower)alkyl or a heterocyclic group (e.g. formyl, acetyl, propionyl, butyryl, isobutyryl, pentanoyl, hexanoyl, 3,3-dimethylbutanoyl, 3-hydroxy-3-methylbutanoyl, 3-oxo-butanoyl, 3-methoxycarbonylpropanoyl, 3-carboxypropanoyl, 4-methoxycarbonylbutanoyl,
25 4-carboxybutanoyl, methylthioacetyl, (1-methylimidazol-2-yl)thioacetyl, hydroxyacetyl, methoxyacetyl, ethoxyacetyl, 3-methoxybutanoyl, chloroacetyl, morpholinoacetyl, piperidinylacetyl, 4-methylpiperidin-1-ylacetyl, 4-hydroxypiperidinyl, pyrrolidinylacetyl, 4-(pyrimidin-2-yl)piperidinylacetyl, 3-hydroxypyrrolidinylacetyl,
30 oxolan-4-ylacetyl, and so on);

(2) cyclo(lower)alkanecarbonyl (e.g. cyclopropylcarbonyl, cyclobutylcarbonyl, cyclopentylcarbonyl, cyclohexylcarbonyl, and so on);

35 (3) lower alkenoyl (e.g. acryloyl, methacryloyl, crotonoyl,

- 19 -

3-methylbutanoyl, and so on);



is hydrogen, hydroxy, lower alkoxy, arylsulfonyl, a heterocyclic group, lower alkyl optionally substituted with lower cycloalkyl or a heterocyclic group, or the like, in addition to their significances above, R^5 and R^6 , together with the nitrogen atom to which they are attached, may represent a heterocyclic group), such as carbamoyl, N-methylcarbamoyl, N,N-dimethylcarbamoyl, N-ethylcarbamoyl, N,N-diethylcarbamoyl, N-propylcarbamoyl, N-phenylsulfonylcarbamoyl, N-methoxycarbamoyl, N-(tetrazol-5-yl)carbamoyl, 1-pyrrolidinylcarbonyl, piperidinocarbonyl, 4-methyl-1-piperazinylcarbonyl, 4-cyclohexyl-1-piperazinylcarbonyl, morpholinocarbonyl, 4-thiomorpholinylcarbonyl, or the like.

The aromatic acyl may include aroyl optionally substituted with one or more suitable substituent(s) such as nitro (e.g. benzoyl, naphthoyl, nitrobenzoyl, and so on), or the like.

The aliphatic acyl substituted with aryl may include ar(lower)alkanoyl which may have one or more suitable substituent(s) such as lower alkoxy (e.g. phenylacetyl, 4-methoxyphenylacetyl, and so on) or the like.

Suitable "arylsulfonyl" may include phenylsulfonyl, tosyl, methoxyphenylsulfonyl, or the like.

Suitable "leaving group" may include hydroxy, halogen, acyloxy, in which the halogen and the acyl moiety may be those as exemplified above, or the like.

The starting compound (II) is prepared in similar manners to those of the below-mentioned Preparations.

- 20 -

Suitable salts of the compounds (I), (I-1) to (I-36) and (II) to (VII) may include pharmaceutically acceptable salts such as basic salts, for example, alkali metal salt (e.g. sodium salt, potassium salt, etc.), alkaline earth metal salt (e.g. calcium salt, magnesium salt, etc.), ammonium salt, amine salt (e.g. triethylamine salt, N-benzyl-N-methylamine salt, etc.) and other conventional organic salts, or acid addition salts, for example, hydrochloride, hydrobromide, sulfate or bisulfate, phosphate or hydrogen phosphate, acetate, benzoate, succinate, fumarate, maleate, lactate, citrate, tartrate, gluconate, methanesulfonate, benzenesulfonate, p-toluenesulfonate, or the like.

The processes for preparing the object compound (I) are explained in detail in the following.

Process 1

The compound (I) or its salt can be prepared by reacting the compound (II) or its salt with the compound (III) or its salt.

This reaction is usually carried out in the presence of an inorganic or an organic base.

Suitable inorganic base may include an alkali metal [e.g., sodium, potassium, etc.], an alkali metal hydroxide [e.g., sodium hydroxide, potassium hydroxide, etc.], alkali metal hydrogen carbonate [e.g., sodium hydrogen carbonate, potassium hydrogen carbonate, etc.], alkali metal carbonate [e.g., sodium carbonate, etc.], alkali earth metal carbonate [calcium carbonate, etc.], or the like.

Suitable organic base may include tri(lower)alkylamine [e.g. triethylamine, N,N-diisopropylethylamine, etc.], alkyl lithium [e.g. methyl lithium, butyl lithium, etc.], lithium diisopropylamide, lithium hexamethyldisirazido, alkali metal hydride [e.g., sodium hydride, potassium hydride, etc.] or the like.

- 21 -

The reaction is usually carried out in a conventional solvent such as water, alcohol [e.g., methanol, ethanol, isopropyl alcohol, etc.], tetrahydrofuran, dioxane, toluene, methylene chloride, chloroform, N,N-dimethylformamide or any
5 other organic solvents which do not adversely affect the reaction, or the mixture thereof.

The reaction temperature is not critical and the reaction is usually carried out under cooling to warming.

10 Process 2

The object compound (I-2) or its salt can be prepared by subjecting a compound (I-1) to deesterification.

The reaction is carried out in accordance with a conventional method such as hydrolysis, reduction or the
15 like.

The hydrolysis is preferably carried out in the presence of a base, an acid, or the combination of Lewis acids and Lewis bases.

Suitable base may include an inorganic base and an
20 organic base.

Suitable inorganic base may be the same as those exemplified in Process 1.

Suitable organic base may include tri(lower)alkylamine [e.g. trimethylamine, triethylamine, etc.], picoline,
25 1,5-diazabicyclo[4.3.0]non-5-ene,
1,4-diazabicyclo[2.2.2]octane,
1,8-diazabicyclo[5.4.0]undec-7-ene, or the like.

Suitable acid may include an organic acid [e.g. formic acid, acetic acid, propionic acid, trichloroacetic acid, trifluoroacetic acid, etc.], an inorganic acid [e.g.
30 hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, etc.].

The hydrolysis is also carried out in the presence of the combination of Lewis acids and Lewis bases.

35 Suitable Lewis acid may include metal halide [e.g.,

- 22 -

aluminum chloride, aluminum bromide, titanium(IV) chloride, tin(IV) chloride, etc.], metal alkoxide [e.g., titanium(IV) isopropoxide, etc.] or the like.

Suitable Lewis base may include lower alkyl thiol [e.g.,
5 ethanethiol, ethanedithiol, etc.], di(lower)alkyl sulfide [dimethylsulfide, etc.], or the like.

The reaction is usually carried out in a solvent such as water, an alcohol [e.g. methanol, ethanol, etc.], xylene, diethylene glycol monomethyl ether, methylene chloride,
10 tetrahydrofuran, a mixture thereof or any other solvent which does not adversely influence the reaction. A liquid base or acid can be also used as the solvent.

The reaction temperature is not critical and the reaction is usually carried out under cooling to warming.

15 The reduction can be applied preferably for elimination of the ester moiety such as 4-nitrobenzyl, 2-iodoethyl, 2,2,2-trichloroethyl, or the like. The reduction method applicable for the elimination reaction may include chemical reduction and catalytic reduction.

20 Suitable reducing agents to be used in chemical reduction are a combination of metal [e.g. tin, zinc, iron, etc.] or metallic compound [e.g. chromium chloride, chromium acetate, etc.] and an organic or inorganic acid exemplified above.

25 Suitable catalysts to be used in catalytic reduction are conventional ones such as platinum catalyst [e.g. platinum on carbon, platinum oxide, etc.], palladium catalyst [e.g. palladium black, palladium oxide, palladium on carbon, etc.] or any other catalyst ordinary employed in the field of
30 organic synthetic chemistry. The catalytic reduction may be carried out in the presence of hydrogen or hydrogen donor such as formic acid, ammonium formate, cyclohexene, or the like.

The reduction is usually carried out in a conventional
35 solvent which does not adversely influence the reaction such

- 23 -

as water, an alcohol [e.g. methanol, ethanol, propanol, etc.], N,N-dimethylformamide, or a mixture thereof.

Additionally, in case that the above-mentioned acids to be used in chemical reduction are in liquid, they can also be used as a solvent. Further, a suitable solvent to be used in catalytic reduction may be the above-mentioned solvent, and other conventional solvent such as diethyl ether, dioxane, tetrahydrofuran, etc., or a mixture thereof.

The reaction temperature of this reduction is not critical and the reaction is usually carried out under cooling to warming.

Process 3

The compound (I-3) or its salt can be prepared by reacting the compound (I-2) or its reactive derivative at the carboxy group, or its salt, with the compound (IV) or its reactive derivative at the amino group, or its salt, according to any well known procedure.

Suitable reactive derivative at the amino group of the compound (IV) may include Schiff's base type imino or its tautomeric enamine type isomer formed by the reaction of the compound (IV) with a carbonyl compound such as aldehyde, ketone or the like; a silyl derivative formed by the reaction of the compound (IV) with a silylating reagent such as trimethylsilyl chloride, N,O-bis(trimethylsilyl)acetamide, N-trimethylsilylacetamide, or the like.

Suitable reactive derivative of the compound (I-2) may include an acid chloride, acid azide, an acid anhydride, an activated amide, an activated ester, or the like.

The suitable acid anhydride may include a mixed acid anhydride with an acid such as substituted phosphoric acid (e.g., dialkylphosphoric acid, phenylphosphoric acid, diphenylphosphoric acid, dibenzylphosphoric acid, halogenated phosphoric acid, etc.), dialkylphosphorous acid, sulfuric acid, thiosulfuric acid, alkanesulfonic acid (e.g.,

- 24 -

methanesulfonic acid, ethanesulfonic acid, etc.), sulfuric acid, alkanolic acid (e.g., pivalic acid, pentanoic acid, isopentanoic acid, etc.), aromatic carboxylic acid (e.g., benzoic acid, chlorobenzoic acid, fluorobenzoic acid, nitrobenzoic acid, etc.), or the like.

Suitable activated amide may be imidazoyleamide, 4-substituted imidazoyleamide, dimethylpyrazoyleamide, triazoyleamide tetrazoyleamide, or the like.

Suitable activated ester may be dimethyliminomethyl [(CH₃)₂N⁺=CH-] ester, vinyl ester, propargyl ester, 4-nitrophenyl ester, 2,4-dinitrophenyl ester, trichlorophenyl ester, pentachlorophenyl ester, pentafluorophenyl ester, methanesulfonylphenyl ester, phenyl thioester, p-nitrophenyl thioester, carboxymethyl thioester, pyranylester, pyridylester, 8-quinolythioester, an ester with a N-hydroxy compound (e.g., N,N-dimethylhydroxylamine, 1-hydroxy-2H-pyridone, N-hydroxysuccinimide, N-hydroxybenzotriazole, N-hydroxyphthalimide, etc.), or the like.

These reactive derivatives can optionally be selected from them according to the kind of compound (I-2) to be used.

When the compound (I-2) is used in free acid form or its salt form in the reaction, the reaction is preferably carried out in the presence of condensing agent.

Suitable condensing agent may include a carbodiimide (e.g., N,N-dicyclohexylcarbodiimide, N-cyclohexyl-N'-(4-diethylaminocyclohexyl)carbodiimide, N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide or its hydrochloride, etc.) diphenylphosphinic azide, diphenylphosphinic chloride, diethylphosphoryl cyanide, bis(2-oxo-3-oxazolidinyl)-phosphinic chloride, N,N'-carbonyldiimidazole, 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline, cyanuric chloride, or the like.

The reaction may be also carried out in the presence of organic or inorganic base such as alkali metal carbonate, tri(lower)alkylamine, pyridine, N-(lower)alkylmorpholine, or

- 25 -

the like.

The reaction is usually carried out in a conventional solvent such as water, acetone, alcohol [e.g., methanol, ethanol, isopropyl alcohol, etc.], tetrahydrofuran, dioxane, toluene, methylene chloride, chloroform, N,N-dimethylformamide or any other organic solvents which do not adversely affect the reaction, or the mixture thereof.

The reaction temperature is not critical and the reaction is usually carried out under cooling to warming.

Process 4

The compound (I-5) or its salt can be prepared by subjecting the compound (I-4) or its salt to deesterification.

This deesterification can be carried out in a similar manner to that of the Process 2, and therefore the reagents to be used and the reaction conditions (e.g., solvent, reaction temperature, etc.) can be referred to those of the Process 2.

Process 5

The compound (I-6) or its salt can be prepared by reacting the compound (I-5) or its reactive derivative at the carboxy group, or its salt, with the compound (IV) or its reactive derivative at the amino group, or its salt.

This reaction can be carried out in a similar manner to that of the Process 3, and therefore the reagents to be used and the reaction conditions (e.g., solvent, reaction temperature, etc.) can be referred to those of the Process 3.

Process 6

The compound (I-8) or its salt can be prepared by reacting a compound (I-7) or its salt with a reducing agent.

Suitable reducing agent may be diborane, sodium borohydride, lithium aluminum hydride or the like.

- 26 -

The reaction is usually carried out in a conventional solvent such as diethyl ether, tetrahydrofuran or any other organic solvent which does not adversely influence the reaction.

5 The reaction temperature is not critical, and the reaction can be carried out under cooling to heating.

Process 7

10 The compound (I-10) or its salt can be prepared by reacting the compound (I-9) or its salt with an acylating agent (V).

15 Suitable acylating agent (V) may be a conventional one used in the Friedel-Crafts acylation reaction such as an acid halide [e.g. acid chloride, acid bromide, etc.], an acid anhydride or the like.

20 This reaction is preferably carried out in the presence of a Lewis acid such as aluminum halide [e.g. aluminum chloride, aluminum bromide, etc.], titanium halide [e.g. titanium tetrachloride, etc.], zinc halide (e.g. zinc chloride), boron trifluoride or the like.

The reaction is usually carried out in a conventional solvent such as carbon disulfide, dichloroethane, tetrachloromethane, benzene or any other organic solvent which does not adversely influence the reaction.

25 The reaction temperature is not critical, and the reaction is usually carried out under cooling to heating.

Process 8

30 The compound (I-12) or its salt can be prepared by subjecting the compound (I-11) or its salt to dehydration at the carbamoyl group.

35 Dehydration is carried out in the conventional manner, which is capable of dehydrating a carbamoyl group to a cyano group, and suitable dehydrating agent may be phosphorus compound (e.g. phosphorous pentoxide, phosphorus

- 27 -

pentachloride, phosphorous oxychloride, pyrocatechyl phosphorus trichloride, and so on); thionyl chloride; or a combination of triaryl phosphine (e.g. triphenyl phosphine, and so on) and chloroform or carbon tetrachloride.

5 The reaction is usually carried out in a conventional solvent such as water, alcohol [e.g., methanol, ethanol, isopropyl alcohol, etc.], tetrahydrofuran, dioxane, toluene, methylene chloride, chloroform, carbon tetrachloride, N,N-dimethylformamide or any other organic solvents which do not
10 adversely affect the reaction, or the mixture thereof.

 The reaction temperature is not critical and the reaction is usually carried out under cooling to warming.

Process 9

15 The object compound (I-13) or its salt can be prepared by reacting a compound (I-12) or its salt with an azide compound.

 Suitable azide compound may be alkali metal azide [e.g. sodium azide, potassium azide, etc.], alkaline earth metal
20 azide [e.g. calcium azide, etc.], aluminum azide, hydrogen azide, trimethyltin azide, or the like.

 The reaction is preferably carried out in the presence of ammonium halide [e.g. ammonium chloride, ammonium bromide, etc.], lower alkylammonium halide [e.g. trimethylammonium
25 chloride, triethylammonium chloride, etc.] or the like.

 The reaction is usually carried out in a conventional solvent such as tetrahydrofuran, dioxane, N,N-dimethylformamide or any other organic solvent which does not adversely influence the reaction.

30 The reaction temperature is not critical, and the reaction can be carried out under warming to heating.

Process 10

 The compound (I-15) or its salt can be prepared by
35 subjecting the compound (I-14) or its salt to

- 28 -

deesterification.

This deesterification can be carried out in a similar manner to that of the Process 2, and therefore the reagents to be used and the reaction conditions (e.g., solvent, reaction temperature, etc.) can be referred to those of the Process 2.

Process 11

The compound (I-16) or its salt can be prepared by subjecting the acid chloride or acid anhydride derived from the compound (I-15) or its salt to intramolecular acylation reaction.

This intramolecular acylation reaction can be carried out in a similar manner to that of the Process 7, and therefore the reagents to be used and the reaction conditions (e.g., solvent, reaction temperature, etc.) can be referred to those of the Process 7.

Process 12

The compound (I-18) or its salt can be prepared by reacting the compound (I-17) or its salt with compound (IV).

This reaction is preferably carried out in the presence of organic or inorganic base exemplified in Process 1, and/or alkali metal iodide (e.g. sodium iodide, potassium iodide, etc.).

The reaction is usually carried out in a solvent such as water, tetrahydrofuran, dioxane, N,N-dimethylformamide or any other solvent which does not adversely influence the reaction.

The reaction temperature is not critical, and the reaction is usually carried out at ambient temperature of under warming to heating.

Process 13

The compound (I-19) or its salt can be prepared by

- 29 -

reacting a compound (I-9) or its salt with a formylating agent.

Suitable formylating agent may be N,N-dimethylformamide; $(\text{CH}_3)_2\text{N}^+=\text{CHCl}\cdot\text{Cl}_2\text{PO}_2^-$ (so-called Vilsmeier reagent prepared by the reaction of N,N-dimethylformamide with phosphorus oxychloride, phosgene, etc.); or the like.

When a formylating agent is N,N-dimethylformamide, the reaction is preferably carried out in the presence of a base such as lower alkyl alkali metal [e.g. n-butyl lithium, ethyl magnesium bromide, etc.], or the like.

The reaction is usually carried out in a solvent such as dioxane, tetrahydrofuran, N,N-dimethylformamide, methylene chloride, chloroform, or any other organic solvent which does not adversely influence the reaction.

The reaction temperature is not critical, and the reaction is usually carried out under cooling to heating.

Process 14

The compound (I-20) or its salt can be prepared by subjecting the compound (I-19) or its salt to oxidation reaction.

Oxidation is carried out in a conventional manner, which is capable of oxidizing formyl group to carboxy group, and suitable oxidizing reagent may be oxygen acid such as periodate (e.g. sodium periodate, potassium periodate, etc.), peroxy acid such as peroxybenzoic acid (e.g., peroxybenzoic acid, m-chloroperoxybenzoic acid, etc.), potassium permanganate, chromic acid, sodium hypochlorite, or the like.

The reaction is usually carried out in a conventional solvent such as water, alcohol (e.g., methanol, ethanol, isopropyl alcohol, etc.), tetrahydrofuran, dioxane, dichloromethane, ethylene dichloride, chloroform, N,N-dimethylformamide, N,N-dimethylacetamide, or any other organic solvent which does not adversely affect the reaction.

Among these solvents, hydrophilic solvents may be used

- 30 -

in a mixture with water.

The reaction temperature is not critical and the reaction is usually carried out under cooling to heating.

5 Process 15

The compound (I-22) or its salt can be prepared by subjecting the compound (I-21) or its salt to a rearrangement reaction.

10 The rearrangement reaction, which is capable of converting the carboxy group into amino group optionally substituted with protected carboxy or acyl (e.g. carbamoyl substituted with lower alkyl, etc.), may be the condition such as Curtius Rearrangement, Hoffmann reaction, Schmidt reaction, or the modification thereof.

15 For example, the Curtius rearrangement consists of the formation of acid azide, the decomposition of acid azide to isocyanate and nitrogen, and the reaction of isocyanate with water, alcohol or amine to afford amine, urethane or urea, respectively.

20 Acid azide can be prepared by treating corresponding acid hydrazide with nitrous acid, treating corresponding acid chloride with alkali metal azide, treating carboxylic acid with diphenylphosphoryl azide, or the like.

25 Acid azide can be rearranged in inert solvent (e.g., toluene, dichloromethane, etc.), from which the isocyanate can be isolated, or in the presence of reagents like alcohol or amine which will react with the intermediate isocyanate to form urethan or urea. Amine or its salt can be obtained by hydrolysis of isocyanate, urethan, or urea.

30 The reaction temperature is not critical and the reaction is usually carried out under cooling to warming.

Process 16

35 The compound (I-24) or its salt can be prepared by reacting the compound (I-23) or its reactive derivative at

- 31 -

the amino group, or its salt, with the compound (VI) or its salt, or the compound (VII) or its salt.

When free acid is used as the compound (VI), the reaction is preferably carried out in the presence of
5 condensing agent exemplified in Process 3.

The reaction is usually carried out in a conventional solvent such as water, alcohol [e.g., methanol, ethanol, isopropyl alcohol, etc.], tetrahydrofuran, dioxane, toluene, methylene chloride, chloroform, N,N-dimethylformamide or any
10 other organic solvents which do not adversely affect the reaction, or the mixture thereof.

The reaction temperature is not critical and the reaction is usually carried out under cooling to warming.

15 Process 17

The compound (I-26) or its salt can be prepared by subjecting a compound (I-25) or its salt to reduction.

The present reduction is carried out by chemical reduction, catalytic reduction, or the like.

20 Suitable reducing agents to be used in chemical reduction are a combination of metal [e.g. tin, zinc, iron, etc.] or metallic compound [e.g. chromium chloride, chromium acetate, etc.] and an organic or inorganic acid [e.g. formic acid, acetic acid, propionic acid, trifluoroacetic acid,
25 p-toluenesulfonic acid, hydrochloric acid, hydrobromic acid, etc.].

Suitable catalysts to be used in catalytic reduction are conventional ones such as platinum catalyst [e.g. platinum, platinum black, platinum oxide, etc.], palladium catalyst
30 [e.g. palladium black, palladium oxide, palladium on carbon, etc.], nickel catalyst [e.g. reduced nickel, nickel oxide, Raney nickel, etc.], cobalt catalyst [e.g. reduced cobalt, Raney cobalt, etc.], iron catalyst [e.g. reduced iron, Raney iron, etc.], copper catalyst [e.g. reduced copper, Raney
35 copper, Ullman copper, etc.] or the like.

- 32 -

The reduction is usually carried out in a conventional solvent which does not adversely influence the reaction such as water, an alcohol [e.g. methanol, ethanol, propanol, etc.], N,N-dimethylformamide, or a mixture thereof.

5 Additionally, in case that the above-mentioned acids to be used in chemical reduction are in liquid, they can also be used as a solvent. Further, a suitable solvent to be used in catalytic reduction may be the above-mentioned solvent and other conventional solvent such as diethyl ether, methylene
10 chloride, dioxane, tetrahydrofuran, etc., or a mixture thereof.

The reaction temperature of this reduction is not critical and the reaction is usually carried out under cooling to warming.

15

Process 18

The compound (I-28) or its salt can be prepared by subjecting a compound (I-27) or its salt to cleavage of ether bond.

20 The cleavage of ether bond is carried out in the presence of an acid including Lewis acid [e.g. hydrochloric acid, hydrobromic acid, hydroiodic acid, boron tribromide, boron trichloride, etc.], tri(lower)alkylsilyliodide [e.g. trimethylsilyliodide, etc.], or any other method ordinary
25 employed in the field of organic synthesis.

The reaction is usually carried out in a solvent such as water, acetic acid, methylene chloride, tetrahydrofuran, a mixture thereof or any other solvent which does not adversely influence the reaction.

30 The reaction temperature is not critical and the reaction is usually carried out under cooling to heating.

Process 19

The compound (I-30) or its salt can be prepared by
35 subjecting the compound (I-29) or its salt to oxidation.

- 33 -

This oxidation can be performed according to the general procedures ordinarily employed in the field of organic chemistry, which is capable of oxidizing a secondary alcohol to ketone, and suitable oxidizing agent is, for example, derivatives of hexavalent chromium(Cr^{VI}) (e.g. chromium trioxide, sodium dichromate, chromium trioxide-dipyridine complex, etc.) or heptavalent manganese(Mn^{VII}) (e.g. potassium permanganate, manganese dioxide, etc.).

The reaction is usually carried out in a conventional solvent such as water, tetrahydrofuran, dioxane, toluene, methylene chloride, chloroform, N,N-dimethylformamide, acetone, or any other organic solvents which do not adversely affect the reaction, or the mixture thereof.

The reaction temperature is not critical and the reaction is usually carried out under cooling to warming.

Process 20

The compound (I-31) or its salt can be prepared by subjecting the compound (I-9) or its salt to halogenation.

This halogenation is usually carried out by using a conventional halogenating agent such as halogen (e.g., chlorine, bromine, etc.), phosphorus trihalide (e.g., phosphorus tribromide, phosphorus trichloride, etc.), phosphorus pentahalide (e.g., phosphorus pentachloride, phosphorus pentabromide, etc.), phosphorus oxychloride (e.g., phosphoryl trichloride, phosphoryl monochloride, etc.), thionyl halide (e.g., thionyl chloride, thionyl bromide, etc.), oxalyl halide (e.g., oxalyl chloride, oxalyl bromide, etc.), sulfuryl halide (e.g., sulfuryl chloride, etc.), pyridinium hydrobromide perbromide, or the like.

This reaction is usually carried out in a solvent such as water, alcohol (e.g., methanol, ethanol, isopropyl alcohol, etc.), benzene, dioxane, N,N-dimethylformamide, tetrahydrofuran, methylene chloride, ethylene dichloride, chloroform, diethyl ether or any other solvent which does not

- 34 -

adversely affect the reaction.

The reaction temperature is not critical and the reaction is usually carried out under cooling to warming.

5 Process 21

The compound (I-32) or its salt can be prepared by reacting a compound (I-9) or its salt with a nitrating agent.

Suitable nitrating agent may be nitric acid, fuming nitric acid, potassium nitrate, nitronium tetrafluoroborate
10 or the like.

The reaction is usually carried out in an acid or an acid anhydride such as sulfuric acid, acetic acid, acetic anhydride or the like.

The reaction temperature is not critical, and the
15 reaction is usually carried out under cooling to heating.

Process 22

The compound (I-33) or its salt can be prepared by subjecting the compound (I-7) or its salt to reduction.

20 This reduction can be performed according to the general procedures ordinarily employed in the field of organic chemistry, which is capable of reducing a ketone to a secondary alcohol, and suitable reducing agent is, for example, metal hydride such as aluminum hydrides (e.g.
25 lithium aluminum hydride, lithium di(lower)alkylaluminum hydride, Red-Al[®], etc.), boron hydrides (e.g. sodium borohydride, sodium borocyanohydride, etc.), or the like.

The reaction is usually carried out in a conventional solvent such as water, tetrahydrofuran, dioxane, toluene,
30 methylene chloride, chloroform, N,N-dimethylformamide, acetone, or any other organic solvents which do not adversely affect the reaction, or the mixture thereof.

The reaction temperature is not critical and the reaction is usually carried out under cooling to warming.

- 35 -

Process 23

The compound (I-35) or its salt can be prepared by reacting a compound (I-34) or its salt with hydroxylamine or its salt.

5 The reaction is usually carried out in a conventional solvent such as water, an alcohol [e.g. methanol, ethanol, etc.], acetone, dioxane, acetonitrile, chloroform, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, dioxane or any other organic solvent
10 which does not adversely influence the reaction. These conventional solvents may also be used in a mixture with water.

The reaction is preferably carried out in the presence of an inorganic or organic base exemplified in Process 1.

15 The reaction temperature is not critical, and the reaction is usually carried out under cooling to heating.

Process 24

20 The compound (I-37) or its salt can be prepared by reacting the compound (I-36) or its reactive derivative at the amino group, or its salt with the compound (VI) or compound (VII).

25 This reaction can be carried out in a similar manner to that of Process 16 and therefore the reagents to be used and the reaction conditions (e.g. reaction temperature, etc.) can be referred to those of the Process 16.

30 The compounds (I) and pharmaceutically acceptable salts thereof of the present invention possess inhibitory activity of cGMP-PDE (especially PDE-V), relaxant activity of smooth muscle, bronchodilator activity, vasodilative activity, inhibitory activity of smooth muscle cells proliferation, inhibitory activity of allergy, and so on.

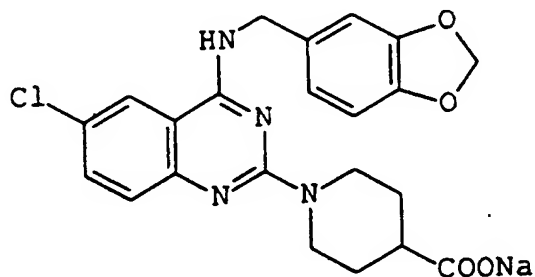
35 The compounds (I) and pharmaceutically acceptable salts thereof, therefore, have utility in the treatment and

- 36 -

prevention of various diseases, such as angina, hypertension, pulmonary hypertension, congestive heart failure, glomerular diseases (e.g. diabetic glomerulosclerosis, etc.), renal tubulo-intestinal diseases (e.g. nephropathy induced by FK506, cyclosporins, or the like), renal failure, atherosclerosis, conditions of reduced blood vessel patency (e.g., post-percutaneous transluminal coronary angioplasty), peripheral vascular disease, stroke, chronic reversible obstructive lung diseases (e.g. bronchitis, asthma (chronic asthma, allergic asthma)), allergic rhinitis, urticaria, glaucoma, diseases characterized by disorders of gut motility (e.g., irritable bowel syndrome), impotence (e.g. organic impotence, psychic impotence, etc.), or diabetic complications (e.g. diabetic gangrene, diabetic arthropathy, diabetic glomerulosclerosis, diabetic dermopathy, diabetic neuropathy, diabetic cataract, diabetic retinopathy, etc.).

Besides the compounds of the formula (I), many compounds, disclosed in various prior publications, are known to have a cyclic nucleotide-PDE inhibitory activity.

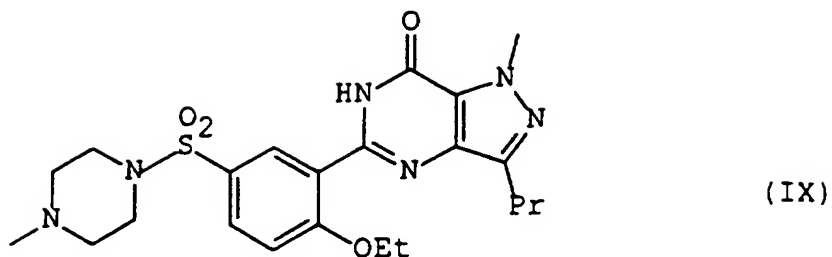
Particularly, a compound having the following formula :



(VIII)

and its analogous compound, and a compound having the following formula :

- 37 -



and its analogous compounds, which have an inhibiting activity of cyclic nucleotide-PDE (especially cGMP-PDE), were known and disclosed in International Patent Publication No. WO 93/07124 and European Patent Publication No. EP 0 526 004. And, various cyclic nucleotide-PDE inhibitors (e.g. papaverine, dipyridamole, etc.) were known and disclosed in Biochemical Pharmacology, vol 46 No. 5, P 833-839.

And further, until now cGMP-PDE inhibitors as exemplified above have been also known to be useful for treating or preventing of various diseases, for example, according to the International Publication No. WO93/07124, angina pectoris, cardiac infarction, ischemic heart disease, for example, chronic and acute cardiac failure, lung hypertension which may be complicated with cor pulmonale, hypertension caused by various factors, peripheral circulatory failure, brain dysfunction, bronchitic asthma and allergic disorder, for example, atopic dermatitis, allergic rhinitis, or the like.

The inventors of this invention have surprisingly found that the cyclic nucleotide-PDE inhibitors are useful for treating or preventing glomerular diseases, renal tubulo-interstitial diseases and chronic renal failure.

According to "International Statistical Classification

- 38 -

of Diseases and Related Health Problems (tenth revision)" (W. H. O., 1992), diseases of genitourinary system are divided into several groups, such as glomerular diseases, renal tubulo-interstitial diseases, renal failure and so on.

Glomerular Diseases are divided into several subgroups, such as rapidly progressive nephritis syndrome, recurrent and persistent haematuria, chronic nephritic syndrome, nephrotic syndrome, glomerular disorders in other diseases, and so on. The diseases, to which glomerular disorder is ascribed, are for example infectious and parasitic diseases; neoplastic diseases; blood diseases and disorders involving the immune mechanism; diabetes mellitus; other endocrine, nutritional and metabolic diseases; systemic connective tissue disorders (e.g. Goodpasture's syndrome, systemic lupus erythematosus, Wegener's granulomatosis, etc.); and so on.

Renal tubulo-interstitial diseases are also divided into several subgroups, one of which is drug- and heavy-metal-induced tubulo-interstitial and tubular conditions, and another one of which is renal tubulo-interstitial disorders in other diseases. The former subgroup includes analgesic nephropathy; nephropathy induced by drugs (e.g. FK506, cyclosporins, and so on), medicaments and biological substances; nephropathy induced by unspecified drug, medicament and biological substance; nephropathy induced by heavy metals; and toxic nephropathy. In the latter subgroup, the diseases, to which renal tubulo-interstitial disorder is ascribed, are for example infectious and parasitic diseases, neoplastic diseases, blood diseases and disorders involving the immune mechanism, metabolic diseases, systematic connective tissue disorders (e.g. sicca syndrome, systematic lupus erythematosus), transplant rejection, and so on.

Renal failure is divided into three subgroups, one of which is chronic renal failure.

The cyclic nucleotide-PDE inhibitors are useful for

- 39 -

treating or preventing glomerular diseases, particularly
glomerular disorders in other diseases, more particularly
glomerular disorders in diabetes mellitus and glomerular
disorders in systemic lupus erythematosus; renal tubulo-
5 interstitial diseases, particularly drug- and heavy-metal-
induced tubulo-interstitial and tubular conditions, and renal
tubulo-interstitial disorders in other disease, more
particularly nephropathy induced by drugs (e.g. FK506,
cyclosporins, and so on), medicaments and biological
10 substances, and renal tubulo-interstitial disorders in
systemic connective tissue disorder; and chronic renal
failure.

The cyclic nucleotide-PDEs include cyclic adenosine
15 3',5'-monophosphate phosphodiesterase (hereinafter described
as cAMP-PDE) and cGMP-PDE. cAMP-PDE and cGMP-PDE play a
major role in the regulation of intracellular concentrations
of cAMP and cGMP, respectively. The cyclic nucleotide-PDEs
are classified into five isozyme families, based largely on
20 primary protein and cDNA sequence information, as follows :
Ca⁺⁺-calmodulin(CaM)-dependent family (Type I); cGMP-
stimulated family (Type II); cGMP-inhibited by a large number
of positive inotropic agents such as milrinone (Type III);
cAMP-specific family, selectively inhibited by rolipram (Type
25 IV); cGMP-specific family, selectively inhibited by zaprinast
(Type V).

The term "immunophilin" is intended to mean a
macromolecular protein or glycoprotein, which is capable of
30 recognizing and selectively binding with immunosuppressive
agent such as FK506, cyclosporins, rapamycins and so on, and
have a peptidyl-propyl cis-trans isomerase activity; for
example, FK506 binding protein (hereinafter indicated as
FKBP) and intracellular receptor to the cyclosporins,
35 preferably, FKBP-12 and cyclophilin produced by mammal, for

- 40 -

example, cattle or man.

Immunophilin is known and is obtained by substantially the same method of J. Am. Chem. Soc., 113, 1409-1411 (1991), Proc. Natl. Acad. Sci. U.S.A., 88, 6229-6233 (1991), Nature
5 346, 671-674 (1991) and 337, 473-475, 476-478 (1989), International Patent Application Nos. 91/17493, 92/01052, Japanese Patent Application No. 2-209897 and so on.

The compound designated as FK506 (or FR-900506) and its analogous compounds are well known to have a potent
10 immunosuppressive activity and are produced by fermentation of the genus streptomyces, especially Streptomyces rukubaensis No. 9993 (FERM BP-927) or Streptomyces hygrosopicus subsp. yakusimaensis No. 7238 (FERM BP-928) (European Patent No. 0184162-B1).

15 The cyclosporins, for example, cyclosporin A, B, C, D, E, F and G, and its derivatives, are disclosed in United State Patent Nos. 4,117,118, 4,215,199, 4,288,431, 4,388,307, Helv. Chem. Acta 60, 1568 (1977) and 65, 1655 (1982), Transplant. Proc., 17, 1362 (1985) and so on, and are well
20 known to have an immunosuppressive activity.

However, FK506 and cyclosporins are also known to induce a renal tubulo-interstitial disease.

25 The cyclic nucleotide-PDE inhibitors can be administered in a pure or impure form and in a single compound or a mixture thereof, preferably, in a pharmaceutical vehicle or carrier.

30 The pharmaceutical composition of this invention can be used in the form of a pharmaceutical preparation, for example, in solid, semisolid or liquid form, which contains the cyclic nucleotide PDE inhibitors, as an active ingredient, in admixture with an organic or inorganic carrier
35 or excipient suitable for external, enteral, intravenous,

- 41 -

intramuscular, or parenteral applications. The active ingredient may be compounded, for example, with the usual non-toxic, pharmaceutically acceptable, carriers for ointment, cream, plaster, tablets, pellets, capsules, 5 suppositories, solutions (saline, for example), emulsion, suspensions (olive oil, for example), and any other form suitable for use. The carriers which can be used are water, wax, glucose, lactose, gum acacia, gelatin, mannitol, starch paste, magnesium trisilicate, talc, corn starch, keratin, 10 paraffin, colloidal silica, potato starch, urea and other carriers suitable for use in manufacturing preparations, in solid, semisolid, or liquid form, and in addition auxiliary, stabilizing, thickening and coloring agents and perfumes may be used. The active compound is included in the 15 pharmaceutical composition in an effective amount sufficient to produce the desired effect upon the process or condition of the diseases.

Mammals which may be treated by the present invention include livestock mammals such as cows, horses, etc., 20 domestic animals such as dogs, cats, rats, etc. and humans, preferably humans.

For applying this composition to a human, it is preferable to apply it by external (topical), oral, parenteral, enteral, intravenous, or intramuscular 25 administration.

While the dosage of therapeutically effective amount of the macrolide compounds varies from and also depends upon the age and condition of each individual patient to be treated, in case of the systemic administration, a daily dose of about 30 0.01-1000 mg, preferably 0.1-500 mg and more preferably 0.5-100 mg of the active ingredient is generally given for treating the diseases, and an average single dose of about 0.2-0.5 mg, 1 mg, 5 mg, 10 mg, 50 mg, 100 mg, 250 mg and 500 mg is generally administered. Daily doses for chronic 35 administration in humans will be in the range of about 0.3

- 42 -

mg/kg/day.

And further, it is considered that the compounds, which have a cyclic nucleotide-PDE inhibitory activity, described in the European Patent Publication Nos. 579,496, 534,443, 526,004, 636,626; United State Patent Nos. 3,819,631, 5,294,612, 5,488,055; International Patent Application Nos. 93/07,124, 94/19,351; Japan Patent Publication No. 07-330,777; and so on, are useful for treating or preventing glomerular diseases, tubulo-interstitial diseases and renal failure.

In order to exhibit the usefulness of the present invention, the activity of compound (I) and the activity of the compound of (VIII) or (IX), papaverine, or dipyridamole, the representative compound of the cyclic nucleotide-PDE inhibitors, is shown in the following.

Test 1.

20

cGMP-Phosphodiesterase (PDE) assay

cGMP-PDE was separated from other isozymes in human platelets by a modification of the method of Thompson et. al. (Cyclic Nucleotide Phosphodiesterase (PDE), in Methods of Enzymatic analysis, Vol 4, pl27-234, 1984). In enzyme inhibition assays, the test compounds were dissolved in 10% DMSO and then diluted with assay buffer (50 mM Tris-HCl, pH 8.0, 0.1 mM dithiothreitol, 2 mM EGTA and 10 u/ml snake venom), at final concentrations ranging from 10^{-10} to 10^{-6} M. Assays were performed at 0.1 μ M substrate ($[^3\text{H}]$ -cGMP) concentration, at 30°C for 10 minutes using enzyme dilutions which gave 10-20% hydrolysis of substrate. Each assay was initiated by addition of substrate and terminated by addition of anion exchange resin (Dowex 1-X8, 25 μ g/mg) followed by centrifugation for 10 minutes (3000 rpm, at 4°C).

- 43 -

Radioactivity of supernatant (^3H -GMP) was assayed by liquid scintillation counting.

The compounds prepared in the present Examples 3, 4, 6,
5 9, 12, 15, 18, 21, 22-(2) to 22-(4), 22-(6), 23, 24-(1),
25-(2), 26, 27-(2), 27-(5), 27-(8), 37-(3), 37-(4), 37-(6),
37-(7), 37-(9), 37-(11), 37-(12), 37-(14), 37-(17), 38-(2),
39, 42, 43, 58, 60, 63, 67-(2), 69, 70, 72, 73-(33), 73-(36),
73-(40), 75-(4), 75-(8), 75-(10), 75-(15), 75-(21), 75-(23),
10 75-(27), 75-(29), 75-(30), 75-(35), 75-(38) and 75-(39),
which were selected as the representative compounds of the
present invention, had IC_{50} values below 100 nM.

Test 2.

15

Smooth muscle relaxant

The aorta were carefully removed from male Wistar rats,
cleaned of fat and extraneous tissue. Spirally cut strips of
the aorta were placed in a 25 ml organ bath containing Tyrode
20 solution of the following composition (mM); NaCl, 137; KCl,
2.7; CaCl_2 , 1.8; NaH_2PO_4 , 0.4; NaHCO_3 , 12.0; MgSO_4 , 1.1;
glucose, 5.6. The bath was maintained at 37°C and bubbled
with 95% O_2 and 5% CO_2 . The spirally cut strip was stretched
to a resting force of 1.0 g, and the isometric contraction
25 was recorded via a force development transducer on an ink
writing recorder. Tissues were equilibrated for 60 minutes
before contraction was induced by noradrenaline (NA, $1\text{ }\mu\text{M}$).
The test compounds were cumulatively added to organ bath in
increasing concentrations ranging from 10^{-8} to 10^{-5} M, after
30 maximum stable constriction to NA had been achieved.

For example, the compounds prepared in the present
Examples 6, 12, 27-(8), 37-(4), 37-(7), 37-(9), 37-(12), 43,
72, 73-(33), 73-(36) and 75-(8), which were selected as the
35 representative compounds of the present invention, had IC_{50}

- 44 -

values below 100 nM.

Test 3.

5 vSMC proliferation

Vascular smooth muscle cells (vSMCs) were prepared from explants of the thoracic aorta of 10 week old male Wistar rats by a modification of the method of Ross (J. Cell Biol., 50: 172, 1971). They were cultured in DMEM containing 10% fetal calf serum, 1% penicillin G and 1% streptomycin at 37°C in a 95% air, 5% CO₂ humidified atmosphere. vSMCs were seeded in 24 well plates and cultured in the presence of 10% fetal calf serum for 3 days. Cell growth then was arrested by transfer to serum free DMEA. After 24 hours, each test compound or vehicle was added to medium for 1 hour, and then cells were stimulated by PDGF (10 ng/ml). After 24 hours of additional incubation, [³H]-thymidine (1 µCi/ml) was added during the final 4 hours of incubation time, and trichloroacetic acid insoluble radioactivity was assayed by liquid scintillation counting.

For example, the compounds prepared in the present Examples 3, 9, 15, 22-(6), 23, 24-(1), 27-(5), 27-(8), 37-(14), 38-(2), 60, 67-(2), 75-(29) and 75-(30), which were selected as representative compounds of the present invention, had IC₅₀ below 100 nM.

Test 4.

30 Vasopressin induced-vasospasm model

Male Donryu rats, weighing 160-200 g, were anesthetized intraperitoneally with sodium pentobarbital (60 mg/kg) 15 minutes before intravenous administration of vasopressin, and the femoral vein was cannulated with polyethylene tubing (diameter 0.8 mm). Coronary vasospasm was induced with

- 45 -

vasopressin (0.2 iu/kg) dissolved in saline through the cannula in the femoral vein. The each test compound (10 mg/kg) was administered orally 30 minutes before the administration of vasopressin. The standard limb lead II of the electrocardiogram was recorded with an electrocardiograph. The depression of ST segment was measured as the difference in the amplitudes of the ST segment after and just before the administration of vasopressin. The amplitudes of ST segment were measured at intervals of 0.5 minutes for 5 minutes after administration of vasopressin.

For example, the compounds prepared in the present Examples 3, 6, 12, 37-(12), 38-(1), 42 and 43 of the present invention, showed more than 50% inhibiting activity, respectively.

Test 5.

20 Cyclosporin nephritis model

Spontaneously hypertensive rats weighing 250-300 g were used. Cyclosporin dissolved in olive-oil containing 5% ethanol was given orally to the animals in a daily dose 50 mg/kg for 2 weeks. After the last dosing of cyclosporin, 24-hours urine was collected for urinalysis. Blood was withdrawn from the abdominal aorta under ether anesthesia 24 hours after the last dosing of cyclosporin, and plasma was separated by centrifugation for biochemical analysis. The animal were bled to death and kidneys were removed for histopathological examination.

The each test compound (3.2 mg/kg) was dissolved in PEG 400 and given orally by the volume of 1 ml/kg twice a day for two weeks.

Biochemistry and urinalysis : Urine volume, plasma creatinine, urine creatinine, blood urea nitrogen, plasma

- 46 -

sodium, urine sodium, plasma potassium and urine potassium, were measured with an autoanalyzer (TBA-20R Toshiba, OM-6020 Daiichi Kagaku).

5 Histopathology : The kidneys were fixed in phosphate-buffered 10% formalin and its paraffin specimens were prepared and these sections were stained with hematoxylin.

The compound (VIII), the compound (IX), and the compounds prepared in the present Examples 3 and 6, which were selected as representative compounds of the present invention, showed more than 50% recovery in a measure of
10 blood urea nitrogen, and more than 40% recovery in a measure of creatinine clearance (ml/kg/min), respectively.

Test 6.

15

FK506 nephritis model

(a) Spontaneously hypertensive rats weighing 250-300 g were used. FK506 dissolved in olive-oil containing 5% ethanol was given orally to the animals in a daily dose 18 mg/kg for 1
20 week. After the last dosing of FK506, 24-hours urine was collected for urinalysis. Blood was withdrawn from the abdominal aorta under ether anesthesia 24 hours after the last dosing of FK506, and plasma was separated by centrifugation for biochemical analysis.

25 The each test compound was dissolved in PEG 400 and given orally by the volume of 1 ml/kg twice a day for two weeks.

Biochemistry and urinalysis : Urine volume, plasma creatinine, urine creatinine, blood urea nitrogen, plasma
30 sodium, urine sodium, plasma potassium and urine potassium, were measured with an autoanalyzer (TBA-20R Toshiba, OM-6020 Daiichi Kagaku).

The compound (VIII) and the compound prepared in Example 6, which was selected as representative compounds of this
35 invention, showed more than 50% recovery in urinary sodium

- 47 -

excretion, and more than 45% recovery in a measure of creatinine clearance (ml/kg/min), respectively.

5 (b) Prevention of experimental FK506-induced nephritis by cyclic nucleotide regulating drugs

FK506 was administered orally to male Sprague-Dawley rats (body weights; 292-329 g) fed with low sodium diet (0.05% Sodium) in a daily dose of 10 mg/kg/day for 14 days.
10 FK506 was provided in a solid dispersion formulation and dissolved in distilled water to a final concentration of 2 mg/ml. Papaverine was dissolved in saline to 5 mg/ml. Dipyridamole (i.v. formulation; 5 mg/ml) was purchased from Dainippon Pharmaceutical Co., Ltd. Papaverine (20 mg/kg) or
15 dipyridamole (20 mg/kg) was administered intramuscularly 30 minutes before FK506 dosing. After the final dosing of FK506, 24-hours urine was collected for urinalysis. Blood was withdrawn from the abdominal aorta under ether anesthesia 24 hours after final dosing of FK506, and plasma was
20 separated for biochemical analysis and plasma renin activity measurements. The kidney was removed from each animal and was fixed with in 10% formalin solution for histological analysis.

25 Papaverine and dipyridamole significantly improved renofunction of FK506 dosed rats. Both compounds showed more than 50% recovery in a measure of blood urea nitrogen, and more than 50% recovery in a serum creatinine.

30 Test 7.

Diabetic glomerulosclerosis model

6 weeks old Male SD rats were treated with streptozotocin (60 mg/kg i.v.) to induce diabetes mellitus.
35 One week after streptozotocin treatment, test compound, 3.2,

- 48 -

10 mg/kg was started to be orally administered twice a day for 16 weeks.

5 The compound prepared in Example 6, which was selected as representative compound of this invention, retarded the onset of diabetic cataract and improved the parameters reflecting the abnormalities of peripheral circulation (improved the decreased blood flow in ears and raised the decreased skin temperature on foot pad).

10 Said compound, 10 mg/kg, perfectly recovered the reduced valiance of RR intervals in cardioelectrography, reduced on average by 37% the elimination of protein in urine, and perfectly inhibited the increased 4-hydroxyproline contents in renal cortex.

15 Test 8.

Impotence model

(a) Effect of test compound on nitroprusside or Ach-induced relaxation in isolated rat corpora cavernosa

20

Male SD rats were anesthetized with sodium pentobarbital 50 mg/kg intraperitoneally, and the corpora cavernosa was excised. The tunica albuginea was dissected according to the methods described by Italiano et al. (Pharmacological Research, 30, No.4, 1994) and used for in vitro
25 pharmacological study. The erectile tissue strip was placed in a 25 ml organ bath containing Krebs-Ringer solution. The bath was maintained at 37°C and bubbled with 95% O₂ and 5% CO₂. The strip was stretched with a resting force of 0.25 g,
30 and isometric contraction were recorded via force development transducer on a recorder.

The strip was equilibrated in the Krebs-Ringer solution for about 60 minutes, and preconstructed by 0.1 mM norepinephrine to ascertain the responsibility of each
35 preparation. The strip was washed several times, and then

- 49 -

constricted by 0.1 mM norepinephrine. After getting stable constrictile response to norepinephrine, the first dose-response curve for sodium nitroprusside or Ach was obtained. After washing a few times for 60 minutes, the strip was
5 constricted by norepinephrine again, and the second dose-response curve for sodium nitroprusside or Ach was obtained. The test compound was added 30 minutes before adding norepinephrine. The compound prepared in Example 6, which was selected as representative compound of this invention, at
10 10^{-7} M potentiated nitroprusside-induced relaxation of corpora cavernosa, and ED_{50} value of dose-response curve to nitroprusside was about 50 μ M.

Said compound at 10^{-7} M also potentiated Ach-induced relaxation of corpora cavernosa. 100 μ M Ach-induced relaxant
15 response to the contractile response induced by 10^{-4} M norepinephrine was only 11.0% in control preparation, but this relaxant response to Ach increased to 18.7% in the presence of 10^{-7} M said compound.

20 (b) Effect of test compound on the relaxation elicited by electrical field stimulation in rat corpora cavernosa.

The rat erectile tissue strip prepared according to the method described by Italiano et al. (Pharmacological
25 Research, 30, No4, 1994) was placed 25 ml organ bath containing Krebs-Ringer solution. The bath was maintained at 37°C and bubbled with 95% O_2 and 5% CO_2 . The solution also contained atropine (1 μ M) and guanethidine (50 μ M). The erectile tissue strip was stretched with a resting force of
30 0.25 g, and isometric contraction were recorded via force development transducer on a recorder. The bipolar platinum electrode connected to the electric stimulator was placed around the strip.

35 The strip was equilibrated in the Krebs-Ringer solution

- 50 -

for about 60 minutes and preconstructed by 0.1 mM norepinephrine to ascertain the responsibility of each preparation. The strip was washed several times, and then constricted by 0.1 mM norepinephrine. After getting stable contractile response to norepinephrine, the first electrical field stimulation (1 to 45Hz, 20V, 0.5 msec duration, 90 sec interval) was delivered. 30 minutes after adding the tested compound, the second electrical field stimulation was delivered.

10 The compound prepared in Example 6, which was selected as representative compound of this invention, at 10^{-7} M potentiated relaxation of corpora cavernosa elicited by electrical field stimulation in rat corpora cavernosa.

15 Relaxant response elicited by 30Hz was only 14.3% in control preparation, but this relaxant response increased to 17.1% in the presence of 10^{-7} M said compound.

(c) Male beagle weighing 8.0 - 12.0 kg were anesthetized with pentobarbital sodium (35 mg/kg, i.v.). After tracheotomy, the animal was artificially ventilated using a volume-cycled ventilator. The femoral artery was cannulated for continuous blood pressure and heart rate monitoring. The femoral vein was cannulated for maintenance of anesthesia and administration of tested compound. Two laser-doppler probes were placed in the corpus spongiosum penis and corpus cavernosum penis for recording blood flow. After a period of stabilization of all parameters, tested compound was injected intravenously at a various concentration. The administration of the compound prepared in Example 6, which was selected as representative compound of this invention, increased in the blood flow of both corpus spongiosum penis and corpus cavernosum penis without hemodynamic change. The increase in blood flow reached a peak value of 55% of baseline and continued for longer than 15 minutes after the administration of said compound 1.0 mg/kg.

20
25
30
35

- 51 -

- (d) Effect of tested compound on genital grooming and penile erection in male mice.

5 Eight weeks old male ICR mice were housed under standard conditions of temperature, lighting and water supply before the experiment.

The test compound was dissolved in PEG400. After oral administration of the test compound, each mouse was transferred to an individual cage.

10 The genital grooming and penile erection were observed for one hour.

The compound prepared in Example 27-(8), which were selected as representative compound of this invention markedly increased the frequencies of genital grooming by
15 average of 266% and lengthened the duration of penile erection by average of 171% (n=10).

Test 9.

20 Toxities of Compound (I)

Test on the toxicity by repetitive oral administration of the compounds prepared in Example 6 and 27-(8), which were selected as representative compound of this invention, in SD rat was conducted and the dead at dose of 32mg/kg once a day
25 for 14 consecutive days could not be observed.

The following preparations and examples are given for the purpose of illustrating the present invention.

30

(to be continued on the next page)

35

- 52 -

Preparation 1

(1) To a solution of 2-amino-4-methoxycarbonylphenyl trifluoromethanesulfonate (2.6 g) in a mixture of pyridine (5.6 ml) and dichloromethane (20 ml) was added benzyl chloroformate (2.08 ml) at 0°C, and the mixture was stirred at 20°C for 4.5 hours. The mixture was diluted with dichloromethane and washed successively with diluted hydrochloric acid, aqueous sodium bicarbonate and brine. The organic layer was dried over sodium sulfate and evaporated in vacuo. The residue was chromatographed on silica gel eluting with dichloromethane to give 2-benzyloxycarbonylamino-4-methoxycarbonylphenyl trifluoromethanesulfonate (2.61 g) as colorless crystals.

NMR (CDCl₃, δ) : 3.92 (3H, s), 5.23 (2H, s), 6.89 (1H, br s), 7.3-7.45 (6H, m), 7.83 (1H, dd, J=1, 8Hz), 8.81 (1H, s)

(2) A mixture of 2-benzyloxycarbonylamino-4-methoxycarbonylphenyl trifluoromethanesulfonate (1.01 g), 1-pentynyl(tributyl)stannane (1.02 g), lithium chloride (0.29 g) and tetrakis(triphenylphosphine)palladium (80 mg) in dioxane (24 ml) was heated at 100°C for 2 hours. The solvent was evaporated in vacuo and the residue was chromatographed on silica gel eluting with a mixture of hexane and ethyl acetate (4:1) to give methyl 3-benzyloxycarbonylamino-4-(1-pentynyl)benzoate (536 mg) as colorless crystals.

NMR (CDCl₃, δ) : 1.03 (3H, t, J=7Hz), 1.67 (2H, m), 2.44 (2H, t, J=7Hz), 3.87 (3H, s), 5.23 (2H, s), 7.25-7.7 (7H, m), 8.78 (1H, s)

(3) To a solution of methyl 3-benzyloxycarbonylamino-4-(1-pentynyl)benzoate (949 mg) in tetrahydrofuran (24 ml) was added gold(III)sodium chloride (24 mg) under argon atmosphere, and the mixture was heated under reflux for 100 minutes. The solvent was evaporated in vacuo and the residue

- 53 -

was chromatographed on silica gel eluting with a mixture of hexane, dichloromethane, and ethyl acetate (6:3:2) to give methyl 1-benzyloxycarbonyl-2-propylindole-6-carboxylate (852 mg) as colorless crystals.

5 NMR (CDCl₃, δ) : 0.98 (3H, t, J=7Hz), 1.71 (2H, m),
2.97 (2H, t, J=7Hz), 3.90 (3H, s), 5.49 (2H, s),
6.39 (1H, s), 7.3-7.6 (6H, m), 7.91 (1H, dd, J=1,
8Hz), 8.80 (1H, s)

10 (4) To a solution of methyl 1-benzyloxycarbonyl-2-propylindole-6-carboxylate (200 mg) in a mixture of methanol and ethyl acetate (1:1, 8 ml) was added 10% palladium on carbon (30 mg), and the mixture was stirred under hydrogen atmosphere for 20 minutes. The catalyst was removed by
15 filtration through celite and washed with methanol. The filtrate was evaporated in vacuo to give methyl 2-propylindole-6-carboxylate (112 mg) as colorless crystals.

20 NMR (CDCl₃, δ) : 1.02 (3H, t, J=7Hz), 1.78 (2H, m),
2.76 (2H, t, J=7Hz), 3.93 (3H, s), 6.29 (1H, s),
7.51 (1H, d, J=8Hz), 7.77 (1H, d, J=8Hz), 8.04 (1H, s), 8.15 (1H, br s)

25 (5) To a stirring suspension of aluminum chloride (294 mg) and acetyl chloride (0.08 ml) in dichloromethane (10 ml) was added methyl 2-propylindole-6-carboxylate (200 mg), and the mixture was stirred at 20°C for 1 hour. The resulting mixture was poured onto ice and extracted with ethyl acetate. The combined organic phase was washed with aqueous sodium bicarbonate and brine, then dried over sodium sulfate and
30 evaporated in vacuo. The residue was triturated with isopropyl ether to give methyl 3-acetyl-2-propylindole-6-carboxylate (78 mg) as colorless crystals.

35 NMR (CDCl₃, δ) : 1.02 (3H, t, J=7Hz), 1.81 (2H, m),
2.69 (3H, s), 3.18 (2H, t, J=7Hz), 3.96 (3H, s),
7.93 (1H, dd, J=1, 8Hz), 8.01 (1H, d, J=8Hz), 8.12

- 54 -

(1H, d, J=1Hz), 8.88 (1H, br s)

Preparation 2

5 Methyl 3-isobutyryl-2-propylindole-6-carboxylate (474 mg) was prepared from methyl 2-propylindole-6-carboxylate (700 mg) and isobutyryl chloride (1.01 ml) in a similar manner to that of Preparation 1 (5).

10 NMR (CDCl₃, δ) : 1.04 (3H, t, J=8Hz), 1.28 (6H, d, J=8Hz), 1.83 (2H, sextet, J=8Hz), 3.18 (2H, t, J=8Hz), 3.52 (2H, septet, J=8Hz), 3.96 (3H, s), 7.92 (2H, s), 8.16 (1H, s), 9.13 (1H, br s)

Preparation 3

15 Methyl 3-propionyl-2-propylindole-6-carboxylate (298 mg) was prepared from methyl 2-propylindole-6-carboxylate (500 mg) and propionyl chloride (0.40 ml) in a similar manner to that of Preparation 1 (5).

20 NMR (CDCl₃, δ) : 1.04 (3H, t, J=8Hz), 1.29 (3H, t, J=8Hz), 1.83 (2H, sextet, J=8Hz), 3.06 (2H, q, J=8Hz), 3.20 (2H, t, J=8Hz), 3.96 (3H, s), 7.93 (1H, dd, J=1, 8Hz), 8.00 (1H, d, J=8Hz), 8.15 (1H, d, J=1Hz), 9.22 (1H, s),

Preparation 4

25 (1) Methyl 3-benzyloxycarbonylamino-4-(4-methyl-1-pentynyl)benzoate (2.25 g) was prepared from 2-benzyloxycarbonylamino-4-methoxycarbonylphenyl trifluoromethanesulfonate (3.0 g) and (4-methyl-1-pentynyl)(tributyl)stannane (2.7 g) in a similar manner to that of Preparation 1 (2).

30 NMR (CDCl₃, δ) : 1.05 (6H, d, J=8Hz), 1.88-2.02 (1H, m), 2.40 (2H, d, J=8Hz), 3.90 (3H, s), 5.25 (2H, s), 7.32-7.45 (6H, m), 7.52 (1H, s), 7.66 (1H, d, J=8Hz), 8.78 (1H, s)

35

- 55 -

(2) Methyl 1-benzyloxycarbonyl-2-isobutylindole-6-carboxylate (1.67 g) was prepared from methyl 3-benzyloxycarbonylamino-4-(4-methyl-1-pentynyl)benzoate (2.15 g) in a similar manner to that of Preparation 1 (3).

5 NMR (CDCl₃, δ) : 0.90 (6H, d, J=8Hz), 1.90-2.04 (1H, m), 2.86 (2H, d, J=8Hz), 3.90 (3H, s), 5.48 (2H, s), 6.38 (1H, s), 7.40-7.56 (6H, m), 7.91 (1H, d, J=8Hz), 8.82 (1H, s)

10 (3) Methyl 2-isobutylindole-6-carboxylate (752 mg) was prepared from methyl 1-benzyloxycarbonyl-2-isobutylindole-6-carboxylate (1.5 g) in a similar manner to that of Preparation 1 (4).

15 NMR (CDCl₃, δ) : 0.98 (6H, d, J=8Hz), 1.95-2.08 (1H, m), 2.66 (2H, d, J=8Hz), 3.92 (3H, s), 6.28 (1H, s), 7.53 (1H, d, J=8Hz), 7.76 (1H, d, J=8Hz), 8.08 (1H, s), 8.23 (1H, br s)

20 (4) Methyl 2-isobutyl-3-isobutyrylindole-6-carboxylate (246 mg) was prepared from methyl 2-isobutylindole-6-carboxylate (300 mg) and isobutyryl chloride (0.41 ml) in a similar manner to that of Preparation 1 (5).

25 NMR (CDCl₃, δ) : 0.98 (6H, d, J=8Hz), 1.27 (1H, d, J=8Hz), 2.10-2.23 (1H, m), 3.06 (2H, d, J=8Hz), 3.52 (2H, septet, J=8Hz), 3.96 (3H, s), 7.92 (2H, s), 8.16 (1H, s), 9.02 (1H, s)

Preparation 5

30 (1) Methyl 3-benzyloxycarbonylamino-4-(1-butynyl)benzoate (646 mg) was prepared from 2-benzyloxycarbonylamino-4-methoxycarbonylphenyl trifluoromethanesulfonate (1.82 g) and 1-butynyl(tributyl)stannane (1.51 g) in a similar manner to that of Preparation 1 (2).

35 NMR (CDCl₃, δ) : 1.26 (3H, t, J=7Hz), 2.50 (2H, q, J=7Hz), 3.91 (3H, s), 5.24 (2H, s), 7.3-7.5 (7H,

- 56 -

m), 7.65 (1H, dd, J=1, 8Hz), 8.79 (1H, br s)

(2) Methyl 1-benzyloxycarbonyl-2-ethylindole-6-carboxylate (551 mg) was prepared from methyl 3-benzyloxycarbonylamino-4-(1-butynyl)benzoate (640 mg) in a similar manner to that of Preparation 1 (3).

NMR (CDCl₃, δ) : 1.30 (3H, t, J=7Hz), 3.05 (2H, q, J=7Hz), 3.88 (3H, s), 4.98 (2H, s), 6.92 (1H, s), 7.35-7.60 (6H, m), 7.89 (1H, dd, J=1, 8Hz), 8.79 (1H, s)

(3) Methyl 2-ethylindole-6-carboxylate (306 mg) was prepared from methyl 1-benzyloxycarbonyl-2-ethylindole-6-carboxylate (546 mg) in a similar manner to that of Preparation 1 (4).

NMR (CDCl₃, δ) : 1.38 (3H, t, J=7Hz), 2.82 (2H, q, J=7Hz), 3.91 (3H, s), 6.30 (1H, s), 7.50 (1H, d, J=8Hz), 7.75 (1H, d, J=8Hz), 8.03 (1H, s), 8.14 (1H, br s)

(4) Methyl 2-ethyl-3-propionylindole-6-carboxylate (435 mg) was prepared from methyl 2-ethylindole-6-carboxylate (660 mg) and propionyl chloride (0.62 ml) in a similar manner to that of Preparation 1 (5).

NMR (CDCl₃, δ) : 1.29 (3H, t, J=7Hz), 1.39 (3H, t, J=7Hz), 3.06 (2H, t, J=7Hz), 3.26 (2H, t, J=7Hz), 3.94 (3H, s), 7.24 (1H, s), 7.92 (1H, d, J=8Hz), 7.98 (1H, d, J=8Hz), 8.14 (1H, s), 8.92 (1H, br s)

Preparation 6

(1) Methyl 3-isobutyrylindole-6-carboxylate (618 mg) was prepared from methyl indole-6-carboxylate (500 mg) and isobutyryl chloride (0.84 ml) in a similar manner to that of Preparation 1 (5).

NMR (CDCl₃, δ) : 1.28 (6H, d, J=7Hz), 3.35 (1H, m), 3.96 (3H, s), 7.93-8.06 (2H, m), 8.19 (1H, s), 8.46

- 57 -

(1H, d, J=8Hz), 8.96 (1H, br s)

(2) To a solution of methyl 3-isobutyrylindole-6-carboxylate (146 mg) in tetrahydrofuran (5 ml) was added 1M solution of
5 brane-tetrahydrofuran complex in tetrahydrofuran (1.8 ml),
and the mixture was stirred at 50°C for 1 hour. The
resulting mixture was evaporated in vacuo, and the residue
was quenched with aqueous ammonium chloride and extracted
with ethyl acetate. The organic phase was washed with brine,
10 and dried over sodium sulfate. After evaporation of solvent,
the residue was chromatographed on silica gel eluting with a
mixture of hexane and ethyl acetate (2:1) to give methyl 3-
isobutyrylindole-6-carboxylate (105 mg) as colorless crystals.

NMR (CDCl₃, δ) : 0.94 (6H, d, J=7Hz), 1.98 (1H, m),
15 2.62 (2H, d, J=7Hz), 3.93 (3H, s), 7.12 (1H, s),
7.61 (1H, d, J=8Hz), 7.78 (1H, d, J=8Hz), 8.08 (1H,
s), 8.16 (1H, br s)

(3) Methyl 2-acetyl-3-isobutyrylindole-6-carboxylate (43 mg)
20 was prepared from methyl 3-isobutyrylindole-6-carboxylate (99
mg) and acetyl chloride (0.073 ml) in a similar manner to
that of Preparation 1 (5).

NMR (CDCl₃, δ) : 1.01 (6H, d, J=7Hz), 2.02 (1H, m),
2.69 (3H, s), 2.98 (2H, d, J=7Hz), 3.96 (3H, s),
25 7.73 (1H, d, J=8Hz), 7.79 (1H, d, J=8Hz), 8.11 (1H,
s), 9.09 (1H, br s)

Preparation 7

(1) Methyl 3-acetylindole-6-carboxylate (470 mg) was
30 prepared from methyl indole-6-carboxylate (655 mg) and acetyl
chloride (0.27 ml) in a similar manner to that of Preparation
1 (5).

NMR (DMSO-d₆, δ) : 2.46 (3H, s), 3.88 (3H, s), 7.79
(1H, d, J=8Hz), 8.10 (1H, s), 8.24 (1H, d, J=8Hz),
35 8.52 (1H, s)

- 58 -

(2) Methyl 3-ethylindole-6-carboxylate (327 mg) was prepared from methyl 3-acetylindole-6-carboxylate (470 mg) in a similar manner to that of Preparation 6 (2).

5 NMR (CDCl₃, δ) : 1.33 (3H, t, J=7Hz), 2.78 (2H, q, J=7Hz), 3.93 (3H, s), 7.15 (1H, s), 7.63 (1H, d, J=8Hz), 7.79 (1H, d, J=8Hz), 8.12 (1H, s), 8.14 (1H, br s)

10 (3) Methyl 3-ethyl-2-propionylindole-6-carboxylate (65.7 mg) was prepared from methyl 3-ethylindole-6-carboxylate (184 mg) and propionyl chloride (0.17 ml) in a similar manner to that of Preparation 1 (5).

15 NMR (CDCl₃, δ) : 1.29 (3H, t, J=7Hz), 1.34 (3H, t, J=7Hz), 3.03 (2H, q, J=7Hz), 3.14 (2H, q, J=7Hz), 3.94 (3H, s), 7.73 (1H, d, J=8Hz), 7.79 (1H, d, J=8Hz), 8.13 (1H, s), 9.10 (1H, br s)

Preparation 8

20 (1) 3-Isobutyryl-2-propylindole-6-carboxylic acid (853 mg) was prepared from methyl 3-isobutyryl-2-propylindole-6-carboxylate (935 mg) in a similar manner to that of Example 2.

25 NMR (DMSO-d₆, δ) : 0.95 (3H, t, J=8Hz), 1.14 (6H, d, J=8Hz), 1.72 (2H, sextet, J=8Hz), 3.08 (2H, t, J=8Hz), 3.46 (1H, septet, J=8Hz), 7.76 (1H, d, J=9Hz), 7.92 (1H, dd, J=1, 9Hz), 8.00 (1H, d, J=1Hz)

30 (2) 3-Isobutyryl-2-propylindole-6-carboxamide (853 mg) was prepared from 3-isobutyryl-2-propylindole-6-carboxylic acid (935 mg) in a similar manner to that of Example 6.

35 NMR (DMSO-d₆, δ) : 0.95 (3H, t, J=8Hz), 1.15 (6H, d, J=8Hz), 1.70 (2H, sextet, J=8Hz), 3.07 (2H, t, J=8Hz), 3.46 (1H, septet, J=8Hz), 7.26 (1H, br s), 7.72 (1H, d, J=9Hz), 7.87 (1H, dd, J=1, 9Hz),

BAD ORIGINAL

- 59 -

7.94 (1H, d, J=1Hz)

Preparation 9

5 Methyl 3-benzoyl-2-propylindole-6-carboxylate (289 mg) was prepared from methyl 2-propylindole-6-carboxylate (500 mg) and benzoyl chloride (970 mg) in a similar manner to that of Preparation 1 (5).

10 NMR (CDCl₃, δ) : 0.82 (3H, t, J=8Hz), 1.66 (2H, sextet, J=8Hz), 2.78 (2H, t, J=8Hz), 3.85 (3H, s), 7.29 (1H, d, J=8Hz), 7.49-7.54 (2H, m), 7.60-7.64 (4H, m), 8.02 (1H, s)

Preparation 10

15 To a stirred solution of methyl 2-propylindole-6-carboxylate (911 mg) in acetonitrile (15 ml) was added chlorosulfonylisocyanate (0.6 g) in acetonitrile (1.5 ml) at 0°C. The mixture was stirred at 0°C for 30 minutes, then N,N-dimethylformamide (0.35 g) in acetonitrile (15 ml) was added at 0°C. The resultant mixture was stirred at 20°C for 20 40 minutes, and then poured into water. The mixture was extracted with methylene chloride three times, and the combined organic phase was dried over sodium sulfate and evaporated in vacuo. The residue was chromatographed on silica gel eluting with a mixture of ethyl acetate and hexane 25 (1:3) to give the crystals which were recrystallized from a mixture of ethyl acetate and hexane to give methyl 3-cyano-2-propylindole-6-carboxylate (535 mg) as colorless crystals.

mp : 148.5-150°C

IR (KBr) : 3251, 2218, 1710, 1264, 1218 cm⁻¹

30 NMR (CDCl₃, δ) : 1.07 (3H, t, J=7Hz), 1.89 (2H, sextet, J=7Hz), 3.00 (2H, t, J=7Hz), 3.99 (3H, s), 7.70 (1H, d, J=7.5Hz), 7.95 (1H, d, J=7.5Hz), 8.19 (1H, s), 9.05 (1H, br s)

MASS (m/z) : 243 (M⁺+1), 76 (bp)

35

BAD ORIGINAL

- 60 -

Preparation 11

Methyl 3-acetyl-2-ethylindole-6-carboxylate (106 mg) was prepared from methyl 2-ethylindole-6-carboxylate (237 mg) and acetyl chloride (0.19 ml) in a similar manner to that of

5 Preparation 1 (5).

NMR (CDCl₃, δ) : 1.42 (3H, t, J=7Hz), 2.69 (3H, s),
3.27 (2H, q, J=7Hz), 3.96 (3H, s), 7.93 (1H, d,
J=8Hz), 8.01 (1H, d, J=8Hz), 8.12 (1H, s), 8.93
(1H, br s)

10

Preparation 12

Methyl 2-ethyl-3-isobutyrylindole-6-carboxylate (200 mg) was prepared from methyl 2-ethylindole-6-carboxylate (317 mg) and isobutyryl chloride (0.36 ml) in a similar manner to that

15 of Preparation 1 (5).

NMR (CDCl₃, δ) : 1.28 (6H, d, J=7Hz), 1.38 (3H, t,
J=7Hz), 3.25 (2H, q, J=7Hz), 3.51 (1H, m), 3.94
(3H, s), 7.92 (2H, s), 8.13 (1H, s), 8.92 (1H, br
s)

20

Preparation 13

(1) Methyl 3-benzyloxycarbonylamino-4-(1-propynyl)benzoate (1.34 g) was prepared from 2-benzyloxycarbonylamino-4-methoxycarbonylphenyl trifluoromethanesulfonate (2.1 g) and

25 tributyl(1-propynyl)stannane (2.49 g) in a similar manner to that of Preparation 1 (2).

NMR (CDCl₃, δ) : 2.14 (3H, s), 3.91 (3H, s), 5.24 (2H,
s), 7.35-7.50 (6H, m), 7.65 (1H, d, J=8Hz), 8.82
(1H, s)

30

(2) Methyl 1-benzyloxycarbonyl-2-methylindole-6-carboxylate (1.2 g) was prepared from methyl 3-benzyloxycarbonylamino-4-(1-propynyl)benzoate (1.32 g) in a similar manner to that of

Preparation 1 (3).

35 NMR (CDCl₃, δ) : 2.63 (3H, s), 3.89 (3H, s), 5.50 (2H,

- 61 -

s), 6.38 (1H, s), 7.35-7.56 (6H, m), 7.91 (1H, d, J=8Hz), 8.81 (1H, s)

(3) Methyl 2-methylindole-6-carboxylate (562 mg) was prepared from methyl 1-benzyloxycarbonyl-2-methylindole-6-carboxylate (1.18 g) in a similar manner to that of Preparation 1 (4).

NMR (CDCl₃, δ) : 2.49 (3H, s), 3.92 (3H, s), 6.28 (1H, s), 7.51 (1H, d, J=8Hz), 7.77 (1H, d, J=8Hz), 8.03 (1H, s), 8.12 (1H, br s)

(4) Methyl 3-isobutyryl-2-methylindole-6-carboxylate (142 mg) was prepared from methyl 2-methylindole-6-carboxylate (305 mg) and isobutyryl chloride (0.47 ml) in a similar manner to that of Preparation 1 (5).

NMR (CDCl₃, δ) : 1.26 (6H, d, J=7Hz), 2.81 (3H, s), 3.47 (1H, m), 3.93 (3H, s), 7.92 (1H, d, J=8Hz), 8.09 (1H, s), 8.85 (1H, br s)

20 Preparation 14

(1) Methyl 3-benzyloxycarbonylamino-4-(3-methoxy-1-propynyl)benzoate (4.23 g) was prepared from 2-benzyloxycarbonylamino-4-methoxycarbonylphenyl trifluoromethanesulfonate (7.73 g) and (3-methoxy-1-propynyl)tributylstannane (6.67 g) in a similar manner to that of Preparation 1 (2).

NMR (CDCl₃, δ) : 3.44 (3H, s), 3.91 (3H, s), 4.38 (2H, s), 5.23 (2H, s), 7.3-7.5 (7H, m), 7.69 (1H, d, J=8Hz), 8.82 (1H, s)

30

(2) Methyl 1-benzyloxycarbonyl-2-methoxymethylindole-6-carboxylate (2.14 g) was prepared from methyl 3-benzyloxycarbonylamino-4-(3-methoxy-1-propynyl)benzoate (4.23 g) in a similar manner to that of Preparation 1 (3).

35 NMR (CDCl₃, δ) : 3.44 (3H, s), 3.88 (3H, s), 4.80 (2H,

- 62 -

s), 5.49 (2H, s), 6.70 (1H, s), 7.36-7.58 (6H, m),
7.92 (1H, d, J=8Hz), 8.80 (1H, s)

(3) Methyl 2-methoxymethylindole-6-carboxylate (0.42 g) was
5 prepared from methyl 1-benzyloxycarbonyl-2-
methoxymethylindole-6-carboxylate (2.12 g) in a similar
manner to that of Preparation 1 (4).

NMR (CDCl₃, δ) : 3.41 (3H, s), 3.94 (3H, s), 4.64 (2H,
s), 6.47 (1H, s), 7.59 (1H, d, J=8Hz), 7.80 (1H, d,
10 J=8Hz), 8.11 (1H, s), 8.59 (1H, br s)

(4) Methyl 3-isobutyryl-2-methoxymethylindole-6-carboxylate
(146 mg) was prepared from methyl 2-methoxymethylindole-6-
carboxylate (396 mg) and isobutyryl chloride (0.53 ml) in a
15 similar manner to that of Preparation 1 (5).

NMR (CDCl₃, δ) : 1.26 (6H, d, J=7Hz), 3.48 (1H, m),
3.58 (3H, s), 3.94 (3H, s), 5.03 (2H, s), 7.88 (1H,
d, J=8Hz), 7.96 (1H, d, J=8Hz), 8.18 (1H, s), 9.45
(1H, br s)

20

Preparation 15

(1) To a solution of methyl 2-propylindole-6-carboxylate
(300 mg) in dichloromethane (10 ml) was added a 1M solution
of tin(IV) chloride in dichloromethane (2.76 ml) at 20°C.
25 The mixture was stirred at 20°C for 30 minutes, then
methoxyacetyl chloride (0.25 ml) was added. After stirred at
20°C for 30 minutes, the mixture was partitioned between
ethyl acetate and water. The organic layer was washed with
water and brine, dried over magnesium sulfate, and evaporated
30 in vacuo. The residue was chromatographed on silica gel
eluting with a mixture of ethyl acetate and hexane (1:10-1:1)
to give methyl 3-methoxyacetyl-2-propylindole-6-carboxylate
(135 mg) as pale yellow crystals.

mp : 127-129°C

35 NMR (CDCl₃, δ) : 1.05 (3H, t, J=8Hz), 1.83 (2H,

BAD ORIGINAL

- 63 -

sextet, $J=8\text{Hz}$), 3.02 (2H, t, $J=8\text{Hz}$), 3.57 (3H, s),
3.97 (3H, s), 4.72 (2H, s), 7.83 (1H, d, $J=8\text{Hz}$),
7.95 (1H, d, $J=8\text{Hz}$), 8.18 (1H, s), 9.38 (1H, br s)

- 5 (2) 3-Methoxyacetyl-2-propylindole-6-carboxylic acid (108 mg) was prepared from methyl 3-methoxyacetyl-2-propylindole-6-carboxylate (120 mg) in a similar manner to that of Example 2.

mp : $>250^{\circ}\text{C}$

- 10 NMR (DMSO- d_6 , δ) : 0.97 (3H, t, $J=8\text{Hz}$), 1.74 (2H, sextet, $J=8\text{Hz}$), 3.09 (2H, t, $J=8\text{Hz}$), 3.38 (3H, s), 4.61 (2H, s), 7.75 (1H, d, $J=8\text{Hz}$), 7.91 (1H, d, $J=8\text{Hz}$), 8.00 (1H, s)

- 15 (3) 3-Methoxyacetyl-2-propylindole-6-carboxamide (89 mg) was prepared from 3-methoxyacetyl-2-propylindole-6-carboxylic acid (95 mg) in a similar manner to that of Example 6.

mp : $165-167^{\circ}\text{C}$

- 20 NMR (DMSO- d_6 , δ) : 0.95 (3H, t, $J=8\text{Hz}$), 1.74 (2H, sextet, $J=8\text{Hz}$), 3.06 (2H, t, $J=8\text{Hz}$), 3.38 (3H, s), 4.60 (2H, s), 7.25 (1H, br s), 7.70 (1H, d, $J=8\text{Hz}$), 7.84 (1H, d, $J=8\text{Hz}$), 7.94 (1H, s), 7.97 (1H, br s)

Preparation 16

- 25 To a solution of methyl 2-amino-3-hydroxybenzoate (882 mg) in pyridine (2 ml) was added acetic anhydride (1.2 ml) and the mixture was stirred at 20°C for 18 hours. The reaction mixture was diluted with diisopropyl ether, and the resulting solid was collected and washed with diisopropyl
30 ether. The solid was triturated with diisopropyl ether to give methyl 2-acetamido-3-acetoxybenzoate (1.25 g) as solid.

NMR (CDCl_3 , δ) : 2.18 (3H, s), 2.26 (3H, s), 3.90 (3H, s), 7.27 (1H, t, $J=8\text{Hz}$), 7.39 (1H, d, $J=8\text{Hz}$), 7.83 (1H, d, $J=8\text{Hz}$), 9.09 (1H, br s)

35

BAD ORIGINAL



- 64 -

Preparation 17

The following compounds described in (1) to (4) were prepared in a similar manner to that of Preparation 16.

- 5 (1) Methyl 3-acetamido-4-acetoxybenzoate
NMR (CDCl₃, δ) : 2.21 (3H, s), 2.37 (3H, s), 3.93 (3H, s), 7.22 (1H, d, J=8Hz), 7.83 (1H, d, J=8Hz), 8.22 (1H, s)
- 10 (2) Methyl 4-acetamido-3-acetoxybenzoate
NMR (DMSO-d₆, δ) : 2.12 (3H, s), 2.33 (3H, s), 3.84 (3H, s), 7.73 (1H, d, J=2Hz), 7.82 (1H, dd, J=2, 8Hz), 8.22 (1H, d, J=8Hz), 9.64 (1H, s)
- 15 (3) Methyl 3-acetamido-2-acetoxybenzoate
NMR (CDCl₃, δ) : 2.20 (3H, s), 2.43 (3H, s), 3.91 (3H, s), 7.29 (1H, t, J=8Hz), 7.74 (1H, d, J=8Hz), 8.51 (1H, d, J=8Hz)
- 20 (4) Methyl 3-acetamido-4-trifluoromethanesulfonyloxyphenyl-
acetate
mp : 68.5-70°C
IR (KBr) : 3341, 1727, 1699, 1437, 1425 cm⁻¹
NMR (CDCl₃, δ) : 2.24 (3H, s), 3.66 (3H, s), 3.73 (3H, s), 7.11 (1H, dd, J=8, 1Hz), 7.24-7.30 (2H, m),
25 8.19 (1H, s)
MASS (m/z) : 354 (M⁺-1), 149 (bp)

Preparation 18

- 30 To a solution of methyl 2-acetamido-3-acetoxybenzoate (1.72 g) in methanol (9 ml) was added powdered potassium carbonate (1.4 g), and the mixture was stirred for 20 minutes. The resulting solid was removed by filtration and washed with methanol. The filtrate was evaporated in vacuo,
35 and the residue was acidified with 1N hydrochloric acid and

- 65 -

extracted with ethyl acetate. The organic phase was washed with brine, dried over sodium sulfate and evaporated in vacuo. The residue was triturated with a mixture of isopropyl ether and hexane to give methyl 2-acetamido-3-hydroxybenzoate (1.21 g) as solid.

NMR (CDCl₃, δ) : 2.33 (3H, s), 3.93 (3H, s), 7.14 (1H, t, J=8Hz), 7.23 (1H, d, J=8Hz), 7.61 (1H, d, J=8Hz), 9.88 (1H, s)

10 Preparation 19

The following compounds described in (1) to (3) were prepared in a similar manner to that of Preparation 18.

(1) Methyl 3-acetamido-4-hydroxybenzoate

15 NMR (DMSO-d₆, δ) : 2.11 (3H, s), 3.80 (3H, s), 6.93 (1H, d, J=8Hz), 7.56 (1H, d, J=2Hz), 8.47 (1H, s), 9.20 (1H, s)

(2) Methyl 4-acetamido-3-hydroxybenzoate

20 NMR (DMSO-d₆, δ) : 2.14 (3H, s), 3.78 (3H, s), 7.37 (1H, dd, J=2, 8Hz), 7.45 (1H, d, J=2Hz), 8.08 (1H, d, J=8Hz), 9.32 (1H, s)

(3) Methyl 3-acetamido-2-hydroxybenzoate

25 NMR (CDCl₃, δ) : 2.33 (3H, s), 4.97 (3H, s), 6.90 (1H, t, J=8Hz), 7.56 (1H, d, J=8Hz), 7.81 (1H, br s), 8.57 (1H, d, J=8Hz)

Preparation 20

30 To a solution of methyl 2-acetamido-3-hydroxybenzoate (1.2 g) in a mixture of pyridine (1.4 ml) and dichloromethane (2 ml) was added slowly trifluoromethanesulfonic anhydride (1.1 ml) at 0°C. When addition was completed, the mixture was stirred at 20°C for 20 minutes. The resulting mixture
35 was poured into ice and extracted with ethyl acetate. The

- 66 -

organic phase was washed with 1N hydrochloric acid, aqueous sodium bicarbonate and brine, dried over sodium sulfate and evaporated in vacuo. The residue was triturated with a mixture of dichloromethane and hexane to give methyl 2-acetamido-3-trifluoromethanesulfonyloxybenzoate (1.78 g) as solid.

NMR (CDCl₃, δ) : 2.24 (3H, s), 3.93 (3H, s), 7.34 (1H, t, J=8Hz), 7.49 (1H, d, J=8Hz), 7.99 (1H, d, J=8Hz), 8.90 (1H, br s)

10

Preparation 21

The following compounds described in (1) to (4) were prepared in a similar manner to that of Preparation 20.

15 (1) Methyl 3-acetamido-4-trifluoromethanesulfonyloxybenzoate

NMR (CDCl₃, δ) : 2.25 (3H, s), 3.93 (3H, s), 7.37 (1H, d, J=8Hz), 7.92 (1H, m), 8.86 (1H, br s)

(2) Methyl 4-acetamido-3-trifluoromethanesulfonyloxybenzoate

20 NMR (CDCl₃, δ) : 2.27 (3H, s), 3.94 (3H, s), 7.51 (1H, br s), 7.94 (1H, d, J=2Hz), 8.05 (1H, dd, J=2, 8Hz), 8.47 (1H, d, J=8Hz)

(3) Methyl 3-acetamido-2-trifluoromethanesulfonyloxybenzoate

25 NMR (CDCl₃, δ) : 2.23 (3H, s), 3.93 (3H, s), 7.40 (1H, br s), 7.43 (1H, t, J=8Hz), 7.76 (1H, d, J=8Hz), 8.39 (1H, d, J=8Hz)

(4) Methyl 3-nitro-4-trifluoromethanesulfonyloxyphenyl-

30 acetate

mp : 44-45°C

IR (KBr) : 1736, 1544, 1434, 1340 cm⁻¹

NMR (CDCl₃, δ) : 3.75 (2H, s), 3.76 (3H, s), 7.41 (1H, d, J=8Hz), 7.68 (1H, dd, J=8, 1Hz), 8.10 (1H, d,

35

J=1Hz)

BAD ORIGINAL

- 67 -

MASS (m/z) : 343 (M⁺), 135 (bp)Preparation 22

5 The following compounds described in (1) to (3) were prepared from a similar manner to that of Preparation 1 (2).

(1) Methyl 2-acetamido-3-(1-pentynyl)benzoate

10 NMR (CDCl₃, δ) : 1.06 (3H, t, J=7Hz), 1.64 (2H, m),
2.20 (3H, s), 2.43 (2H, t, J=7Hz), 3.88 (3H, s),
7.16 (1H, t, J=8Hz), 7.57 (1H, d, J=8Hz), 7.76 (1H,
d, J=8Hz), 8.42 (1H, br s)

(2) Methyl 4-acetamido-3-(1-pentynyl)benzoate

15 NMR (CDCl₃, δ) : 1.11 (3H, t, J=8Hz), 1.68 (2H,
sextet, J=8Hz), 2.24 (3H, s), 2.52 (2H, t, J=8Hz),
3.89 (3H, s), 7.94 (1H, dd, J=1, 8Hz), 8.07 (1H, d,
J=1Hz), 8.12 (1H, br s), 8.48 (1H, d, J=8Hz)

(3) Methyl 3-acetamido-2-(1-pentynyl)benzoate

20 NMR (CDCl₃, δ) : 1.12 (3H, t, J=7Hz), 1.73 (2H, m),
2.22 (3H, s), 2.59 (2H, t, J=7Hz), 3.91 (3H, s),
7.32 (1H, t, J=8Hz), 7.63 (1H, d, J=8Hz), 8.29 (1H,
br s), 8.62 (1H, d, J=8Hz)

25 Preparation 23

A mixture of methyl 3-acetamido-4-trifluoromethane-sulfonyloxybenzoate (1.43 g), methyl 5-hexynoate (582 mg), palladium(II) chloride (14.9 mg), triphenylphosphine (43.8 mg) and copper(I) chloride (32 mg) in diethylamine (18 ml)
30 was stirred at 20°C for 14 hours. The solvent was evaporated in vacuo and the residue was chromatographed on silica gel eluting with a mixture of hexane and ethyl acetate (1:2) to give methyl 3-acetamido-4-(5-methoxycarbonyl-1-pentynyl)-benzoate (1.15 g) as colorless crystals.

35 NMR (CDCl₃, δ) : 2.02 (2H, m), 2.27 (3H, s), 2.53 (2H,

- 68 -

t, J=7Hz), 2.63 (2H, t, J=7Hz), 3.68 (3H, s), 3.90 (3H, s), 7.41 (1H, d, J=8Hz), 7.70 (1H, d, J=8Hz), 8.00 (1H, br s), 8.98 (1H, br s)

5 Preparation 24

The following compounds described in (1) to (3) were prepared in a similar manner to that of Preparation 23.

(1) Methyl 3-acetamido-4-(1-pentynyl)benzoate

10 NMR (CDCl₃, δ) : 1.12 (3H, t, J=7Hz), 1.65 (2H, m),
2.23 (3H, s), 2.54 (2H, t, J=7Hz), 3.90 (3H, s),
7.43 (1H, dd, J=1, 8Hz), 7.70 (1H, m), 7.95 (1H, br s), 8.98 (1H, br s)

15 (2) Methyl 3-acetamido-4-(4-methoxycarbonyl-1-butynyl)benzoate

NMR (CDCl₃, δ) : 2.32 (3H, s), 2.68 (2H, m), 2.80 (2H, m), 3.73 (3H, s), 3.89 (3H, s), 7.38 (1H, d, J=8Hz), 7.67 (1H, m), 8.28 (1H, br s), 9.04 (1H, br s)

20

(3) Methyl 3-acetamido-4-(1-pentynyl)phenylacetate

mp : 77-78°C

IR (KBr) : 3293, 1739, 1699, 1665, 1428 cm⁻¹

25 NMR (CDCl₃, δ) : 1.09 (3H, t, J=7Hz), 1.69 (2H, sextet, J=7Hz), 2.22 (3H, s), 2.49 (2H, t, J=7Hz), 3.64 (2H, s), 3.70 (3H, s), 6.94 (1H, d, J=7.5Hz), 7.31 (1H, d, J=7.5Hz), 7.93 (1H, br s), 8.33 (1H, s)

30 MASS (m/z) : 274 (M⁺+1, bp)

Preparation 25

The following compounds described in (1) to (7) were prepared in a similar manner to that of Preparation 1 (3).

35

BAD ORIGINAL

- 69 -

(1) Methyl 1-acetyl-2-(3-methoxycarbonylpropyl)indole-6-carboxylate

NMR (CDCl₃, δ) : 2.08 (2H, m), 2.43 (2H, t, J=7Hz),
2.86 (3H, s), 3.12 (2H, t, J=7Hz), 3.67 (3H, s),
3.94 (3H, s), 6.49 (1H, s), 7.52 (1H, d, J=8Hz),
7.93 (1H, d, J=8Hz), 8.47 (1H, s)

(2) Methyl 1-acetyl-2-propylindole-7-carboxylate

NMR (CDCl₃, δ) : 1.04 (3H, t, J=7Hz), 1.78 (2H, m),
2.39 (3H, s), 2.79 (2H, m), 3.91 (3H, s), 6.38 (1H,
m), 7.23 (1H, t, J=8Hz), 7.68 (1H, d, J=8Hz), 7.79
(1H, d, J=8Hz)

(3) Methyl 1-acetyl-2-propylindole-6-carboxylate

NMR (CDCl₃, δ) : 1.06 (3H, t, J=7Hz), 1.77 (2H, m),
2.82 (3H, s), 3.03 (2H, t, J=8Hz), 3.94 (3H, s),
6.47 (1H, s), 7.49 (1H, d, J=8Hz), 7.94 (1H, d,
J=8Hz), 8.53 (1H, s)

(4) Methyl 1-acetyl-2-propylindole-5-carboxylate

NMR (CDCl₃, δ) : 1.05 (3H, t, J=8Hz), 1.75 (2H,
sextet, J=8Hz), 2.76 (3H, s), 2.98 (2H, t, J=8Hz),
3.94 (3H, s), 6.48 (1H, d, J=1Hz), 7.87 (1H, d,
J=8Hz), 7.95 (1H, d, J=8Hz), 8.18 (1H, s)

(5) Methyl 1-acetyl-2-propylindole-4-carboxylate

NMR (CDCl₃, δ) : 1.07 (3H, t, J=7Hz), 1.80 (2H, m),
2.76 (3H, s), 3.01 (2H, t, J=7Hz), 3.97 (3H, s),
7.18 (1H, s), 7.28 (1H, t, J=8Hz), 8.06 (1H, d,
J=8Hz), 8.15 (1H, d, J=8Hz)

(6) Methyl 1-acetyl-2-(2-methoxycarbonylethyl)indole-6-carboxylate

NMR (CDCl₃, δ) : 2.78 (2H, t, J=7Hz), 2.87 (3H, s),
3.39 (2H, t, J=7Hz), 3.68 (3H, s), 3.94 (3H, s),

BAD ORIGINAL

- 70 -

6.49 (1H, s), 7.52 (1H, d, J=8Hz), 7.93 (1H, d, J=8Hz), 8.46 (1H, s)

(7) Methyl 1-acetyl-2-propylindol-6-ylacetate

5

mp : 85-87°C

IR (KBr) : 1736, 1700, 1376, 1320, 1303 cm^{-1}

10 NMR (CDCl_3 , δ) : 1.04 (3H, t, J=7Hz), 1.74 (2H, sextet, J=7Hz), 2.75 (3H, s), 2.96 (2H, t, J=7Hz), 3.70 (2H, s), 3.75 (3H, s), 6.40 (1H, s), 7.14 (1H, d, J=8Hz), 7.43 (1H, d, J=8Hz), 7.81 (1H, s)

MASS (m/z) : 274 ($\text{M}^+ + 1$), 74 (bp)

Preparation 26

15 To a solution of methyl 1-acetyl-2-(3-methoxycarbonylpropyl)indole-6-carboxylate (2.34 g) in methanol (20 ml) was added powdered potassium carbonate (1.04 g), and the mixture was stirred under reflux for 10 minutes. The resulting mixture was evaporated in vacuo and the residue was acidified with 1N hydrochloric acid and extracted with 20 chloroform. The organic phase was washed with aqueous sodium bicarbonate and brine, dried over sodium sulfate and then evaporated in vacuo. The residue was triturated with ether to give methyl 2-(3-methoxycarbonylpropyl)indole-6-carboxylate (1.23 g) as solid.

25 NMR (CDCl_3 , δ) : 2.07 (2H, m), 2.42 (2H, t, J=7Hz), 2.84 (2H, t, J=7Hz), 3.68 (3H, s), 3.92 (3H, s), 6.31 (1H, s), 7.52 (1H, d, J=8Hz), 7.78 (1H, d, J=8Hz), 8.07 (1H, s), 8.39 (1H, br s)

30 Preparation 27

The following compounds described in (1) to (5) were prepared in a similar manner to that of Preparation 26.

(1) Methyl 2-propylindole-7-carboxylate

35

NMR (CDCl_3 , δ) : 1.02 (3H, t, J=7Hz), 1.78 (2H, m),

BAD ORIGINAL

- 71 -

2.78 (2H, t, J=7Hz), 3.98 (3H, s), 6.28 (1H, m),
7.09 (1H, t, J=8Hz), 7.72 (1H, d, J=8Hz), 7.79 (1H,
d, J=8Hz), 9.58 (1H, br s)

5 (2) Methyl 2-propylindole-6-carboxylate

(3) Methyl 2-propylindole-5-carboxylate

NMR (CDCl₃, δ) : 1.02 (3H, t, J=8Hz), 1.76 (2H,
sextet, J=8Hz), 2.74 (2H, t, J=8Hz), 3.92 (3H, s),
10 6.33 (1H, d, J=1Hz), 7.28 (1H, d, J=8Hz), 7.73 (1H,
d, J=8Hz), 8.10 (1H, br s), 8.28 (1H, s)

(4) Methyl 2-propylindole-4-carboxylate

NMR (CDCl₃, δ) : 1.03 (3H, t, J=7Hz), 1.80 (2H, m),
15 2.78 (2H, m), 3.98 (3H, s), 6.89 (1H, s), 7.14 (1H,
t, J=8Hz), 7.48 (1H, d, J=8Hz), 7.84 (1H, d,
J=8Hz), 8.08 (1H, br s)

(5) Methyl 2-(2-methoxycarbonyl)ethylindole-6-carboxylate

NMR (CDCl₃, δ) : 2.78 (2H, m), 3.10 (2H, m), 3.73 (3H,
20 s), 3.93 (3H, s), 6.30 (1H, s), 7.53 (1H, d,
J=8Hz), 7.76 (1H, d, J=8Hz), 8.08 (1H, s), 8.85
(1H, br s)

25 Preparation 28

The following compounds described in (1) to (19) were
prepared in a similar manner to that of Preparation 1 (5).

(1) Methyl 3-isobutyryl-2-propylindole-7-carboxylate

NMR (CDCl₃, δ) : 1.04 (3H, t, J=7Hz), 1.27 (6H, d,
30 J=7Hz), 1.82 (2H, m), 3.26 (2H, m), 3.47 (1H, m),
3.99 (3H, s), 7.28 (1H, t, J=8Hz), 7.85 (1H, d,
J=8Hz), 8.18 (1H, s)

35 (2) Methyl 3-isobutyryl-2-propylindole-5-carboxylate



- 72 -

NMR (CDCl₃, δ) : 1.04 (3H, t, J=8Hz), 1.28 (6H, d, J=8Hz), 1.78 (2H, sextet, J=8Hz), 3.15 (2H, t, J=8Hz), 3.56 (1H, septet, J=8Hz), 3.96 (3H, s), 7.37 (1H, d, J=1Hz), 7.93 (1H, dd, J=1, 8Hz), 8.66 (1H, d, J=8Hz), 8.75 (1H, br s)

(3) Methyl 3-(3-methoxycarbonylpronanoyl)indole-6-carboxylate

NMR (DMSO-d₆, δ) : 2.65 (2H, t, J=7Hz), 3.22 (2H, t, J=7Hz), 3.59 (3H, s), 3.87 (3H, s), 7.80 (1H, d, J=8Hz), 8.10 (1H, s), 8.23 (1H, d, J=8Hz), 8.59 (1H, s)

(4) Methyl 3-acetyl-2-methylindole-6-carboxylate

NMR (CDCl₃, δ) : 2.54 (3H, s), 2.73 (3H, s), 3.86 (3H, s), 7.76 (1H, d, J=8Hz), 7.97 (1H, s), 8.12 (1H, d, J=8Hz)

(5) Methyl 2-methyl-3-propionylindole-6-carboxylate

NMR (CDCl₃, δ) : 1.12 (3H, t, J=7Hz), 2.72 (3H, s), 2.92 (2H, q, J=7Hz), 3.86 (3H, s), 7.75 (1H, d, J=8Hz), 7.96 (1H, s), 8.11 (1H, d, J=8Hz)

(6) Methyl 3-(3,3-dimethylbutanoyl)indole-6-carboxylate

NMR (CDCl₃, δ) : 1.11 (9H, m), 2.33 (2H, s), 3.94 (3H, s), 7.92-8.0 (2H, m), 8.19 (1H, s), 8.52 (1H, d, J=8Hz), 8.90 (1H, br s)

(7) Ethyl 3-isobutyryl-2-propylindol-6-ylacetate

IR (Neat) : 3300, 1740, 1625 cm⁻¹

NMR (CDCl₃, δ) : 1.04 (3H, t, J=7Hz), 1.25 (6H, d, J=7Hz), 1.26 (3H, t, J=7Hz), 1.77 (2H, sextet, J=7Hz), 3.12 (2H, t, J=7Hz), 3.41-3.55 (1H, m), 3.72 (2H, s), 4.16 (2H, q, J=7Hz), 7.17 (1H, d, J=7.5Hz), 7.30 (1H, s), 7.82 (1H, d, J=7.5Hz), 8.40

- 73 -

(1H, br s)

MASS (m/z) : 316 (M^+ +1), 74 (bp)

(8) Methyl 3-isobutyryl-2-propylindol-6-ylacetate

5 IR (Neat) : 3290, 1730, 1625 cm^{-1}

NMR (CDCl_3 , δ) : 1.03 (3H, t, $J=7\text{Hz}$), 1.26 (6H, d, $J=7\text{Hz}$), 1.76 (2H, sextet, $J=7\text{Hz}$), 3.12 (2H, t, $J=7\text{Hz}$), 3.41-3.54 (1H, m), 3.71 (2H, s), 3.75 (3H, s), 7.16 (1H, d, $J=7.5\text{Hz}$), 7.30 (1H, s), 7.83 (1H, d, $J=7.5\text{Hz}$), 8.40 (1H, br s)

10 MASS (m/z) : 302 (M^+ +1, bp)

(9) Methyl 2-acetyl-3-methylindole-6-carboxylate

15 NMR (CDCl_3 , δ) : 2.66 (3H, s), 2.67 (3H, s), 3.94 (3H, s), 7.72 (1H, d, $J=8\text{Hz}$), 7.81 (1H, d, $J=8\text{Hz}$), 8.11 (1H, s), 9.09 (1H, br s)

(10) Methyl 3-propionylindole-6-carboxylate

20 NMR (CDCl_3 , δ) : 1.12 (3H, t, $J=7\text{Hz}$), 2.89 (2H, q, $J=7\text{Hz}$), 3.87 (3H, s), 7.79 (1H, d, $J=8\text{Hz}$), 8.11 (1H, s), 8.28 (1H, d, $J=8\text{Hz}$), 8.53 (1H, s)

(11) Methyl 2-propionyl-3-propylindole-6-carboxylate

25 NMR (CDCl_3 , δ) : 1.06 (3H, t, $J=7\text{Hz}$), 1.29 (3H, t, $J=7\text{Hz}$), 1.74 (2H, m), 2.95-3.13 (4H, m), 3.94 (3H, s), 7.72 (1H, d, $J=8\text{Hz}$), 7.79 (1H, d, $J=8\text{Hz}$), 8.12 (1H, s), 9.11 (1H, br s)

(12) Methyl 2-isobutyryl-3-propylindole-6-carboxylate

30 NMR (CDCl_3 , δ) : 1.04 (3H, t, $J=7\text{Hz}$), 1.29 (6H, t, $J=7\text{Hz}$), 1.76 (2H, m), 3.09 (2H, m), 3.44 (1H, m), 3.94 (3H, s), 7.71 (1H, d, $J=8\text{Hz}$), 7.79 (1H, d, $J=8\text{Hz}$), 8.12 (1H, s), 9.12 (1H, br s)

35 (13) Methyl 3-cyclopropanecarbonyl-2-propylindole-6-



- 74 -

carboxylate

mp : 152.5-154°C

IR (KBr) : 3371, 1687, 1623, 1458 cm⁻¹

5 NMR (CDCl₃, δ) : 1.00-1.09 (2H, m), 1.02 (3H, t, J=7Hz), 1.28-1.32 (2H, m), 1.82 (2H, sextet, J=7Hz), 2.56-2.65 (1H, m), 3.15 (2H, t, J=7Hz), 3.96 (3H, s), 8.00 (2H, AB, J=8, 8Hz), 8.15 (1H, s), 8.89 (1H, br s)

MASS (m/z) : 286 (M⁺+1, bp)

10

(14) Methyl 3-cyclobutanecarbonyl-2-propylindole-6-carboxylate

mp : 159-160°C

IR (KBr) : 1692, 1645, 1623 cm⁻¹

15 NMR (CDCl₃, δ) : 1.06 (3H, t, J=7Hz), 1.83 (2H, sextet, J=7Hz), 1.93-2.13 (2H, m), 2.30-2.51 (4H, m), 3.20 (2H, t, J=7Hz), 3.95 (3H, s), 3.99 (1H, quintet, J=7Hz), 7.93 (2H, s), 8.15 (1H, s), 9.08 (1H, br s)

20 MASS (m/z) : 300 (M⁺+1), 74 (bp)

(15) Methyl 3-cyclopentanecarbonyl-2-propylindole-6-carboxylate

mp : 137-139°C

25 IR (KBr) : 1692, 1647, 1624 cm⁻¹

NMR (CDCl₃, δ) : 1.02 (3H, t, J=7Hz), 1.64-1.82 (6H, m), 1.94-2.05 (4H, m), 3.17 (2H, t, J=7Hz), 3.72 (1H, quintet, J=7Hz), 3.95 (3H, s), 7.93 (2H, ABX, J=8, 8, 1Hz), 8.15 (1H, d, J=1Hz), 9.19 (1H, s)

30 MASS (m/z) : 314 (M⁺+1, bp)

(16) Methyl 3-cyclohexanecarbonyl-2-propylindole-6-carboxylate

mp : 136-137°C

35 IR (KBr) : 1691, 1651, 1487, 1435 cm⁻¹

BAD ORIGINAL

- 75 -

NMR (CDCl₃, δ) : 1.03 (3H, t, J=7Hz), 1.25-2.04 (12H, m), 3.14-3.25 (1H, m), 3.18 (2H, t, J=7Hz), 3.97 (3H, s), 7.90 (2H, q, J=7.5Hz), 8.17 (1H, s), 9.16 (1H, br s)

5 MASS (m/z) : 328 (M⁺+1), 74 (bp)

(17) Methyl 3-(3-methyl-2-butenoyl)-2-propylindole-6-carboxylate

mp : 146-147°C

10 IR (KBr) : 1715, 1464, 1433, 1220 cm⁻¹

NMR (CDCl₃, δ) : 1.05 (3H, t, J=7Hz), 1.82 (2H, sextet, J=7Hz), 2.05 (3H, s), 2.20 (3H, s), 3.18 (2H, t, J=7Hz), 3.94 (3H, s), 6.63 (1H, s), 7.95 (2H, AB, J=7.5, 7.5Hz), 8.11 (1H, s), 8.88 (1H, br s)

15

MASS (m/z) : 300 (M⁺+1), 74 (bp)

(18) Methyl 3-crotonoyl-2-propylindole-6-carboxylate

mp : 153-154°C

20 IR (KBr) : 1715, 1650, 1583, 1567, 1459, 1432 cm⁻¹

NMR (CDCl₃, δ) : 1.05 (3H, t, J=7Hz), 1.83 (2H, sextet, J=7Hz), 2.04 (3H, dd, J=7, 1Hz), 3.15 (2H, t, J=7Hz), 3.96 (3H, s), 6.89 (1H, dd, J=15, 1Hz), 7.04 (1H, dd, J=15, 7Hz), 7.94 (2H, dq, J=7, 1Hz), 8.12 (1H, s), 8.99 (1H, br s)

25

MASS (m/z) : 286 (M⁺+1)

(19) 3-Acetyl-6-chloroindole

NMR (CDCl₃, δ) : 2.44 (3H, s), 7.19 (1H, d, J=8Hz), 7.51 (1H, s), 8.14 (1H, d, J=8Hz), 8.35 (1H, s)

30

Preparation 29

The following compounds described in (1) to (3) were prepared in a similar manner to that of Preparation 6 (2).

35

BAD ORIGINAL

- 76 -

(1) Methyl 3-(3-methoxycarbonylpropyl)indole-6-carboxylate

NMR (CDCl₃, δ) : 2.04 (2H, m), 2.37 (2H, t, J=7Hz),
2.81 (2H, t, J=7Hz), 3.64 (3H, s), 3.93 (3H, s),
7.16 (1H, s), 7.61 (1H, d, J=8Hz), 7.79 (1H, d,
J=8Hz), 8.10 (1H, s), 8.22 (1H, br s)

5

(2) Methyl 3-methylindole-6-carboxylate

NMR (CDCl₃, δ) : 2.33 (3H, s), 3.93 (3H, s), 7.12 (1H,
s), 7.59 (1H, d, J=8Hz), 7.80 (1H, d, J=8Hz), 8.09
(1H, s), 8.10 (1H, br s)

10

(3) Methyl 3-propylindole-6-carboxylate

NMR (CDCl₃, δ) : 1.00 (3H, t, J=7Hz), 1.74 (2H, m),
2.73 (2H, t, J=7Hz), 3.93 (3H, s), 7.14 (1H, d,
J=1Hz), 7.60 (1H, d, J=8Hz), 7.79 (1H, d, J=8Hz),
8.10 (1H, s), 8.18 (1H, br s)

15

Preparation 30

To a solution of methyl 3-(3-methoxycarbonylpropyl)-
indole-6-carboxylate (656 mg) in methanol (24 ml) was added
1N aqueous sodium hydroxide (2.46 ml), and the mixture was
stirred at 20°C for 2 days. The resulting mixture was
evaporated in vacuo, and the residue was acidified with 1N
hydrochloric acid (2.6 ml) and extracted with ethyl acetate.
The organic phase was washed with brine, dried over sodium
sulfate and evaporated in vacuo. The residue was triturated
with ether to give methyl 3-(3-carboxypropyl)indole-6-
carboxylate (486 mg) as solid.

20

25

NMR (CDCl₃, δ) : 2.03 (2H, m), 2.37 (2H, m), 2.80 (2H,
m), 3.93 (3H, s), 7.17 (1H, s), 7.59 (1H, d,
J=8Hz), 7.74 (1H, d, J=8Hz), 8.09 (1H, s)

30

Preparation 31

A mixture of methyl 3-(3-carboxypropyl)indole-6-
carboxylate (173 mg), triphenylphosphine (191 mg) and carbon

35

- 77 -

tetrachloride (1.0 ml) in 1,2-dichloroethane (10 ml) was heated at 80°C for 2 hours. The resulting mixture was diluted with chloroform and washed with water, aqueous sodium bicarbonate and brine. The organic phase was dried over sodium sulfate and evaporated in vacuo. The residue was purified by silica gel thin layer chromatography with a mixture of hexane and ethyl acetate (4:1) and recrystallized from a mixture of hexane and ethyl acetate to give methyl 8-oxo-5,6,7,8-tetrahydrocarbazole-2-carboxylate (72.2 mg) as colorless crystals.

NMR (CDCl₃, δ) : 2.29 (2H, m), 2.69 (2H, t, J=7Hz), 3.03 (2H, t, J=7Hz), 3.94 (3H, s), 7.69 (1H, d, J=8Hz), 7.82 (1H, d, J=8Hz), 8.16 (1H, s), 8.95 (1H, br s)

Preparation 32

To a stirred mixture of methyl (E)-4-[2-(dimethylamino)vinyl]-3-nitrobenzoate (500 mg), which was prepared by the method of Brown et al. described in Journal of Medicinal Chemistry, vol. 35, page 2419 (1992), and pyridine (0.16 ml) in tetrahydrofuran (3 ml) was added butyryl chloride (0.21 ml) at 20°C. The reaction mixture was stirred at 40°C for 24 hours and 50°C for 4 hours. After cooled to 20°C, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic phase was washed with water and brine, dried over magnesium sulfate and evaporated in vacuo. The residue was chromatographed on silica gel eluting with a mixture of ethyl acetate and hexane (1:1) to give methyl 4-(1-dimethylaminomethylene-2-oxopentyl)-3-nitrobenzoate (426 mg) as colorless amorphous.

NMR (CDCl₃, δ) : 0.89 (3H, t, J=7Hz), 1.52-1.65 (2H, m), 2.30 (2H, t, J=7Hz), 2.78 (6H, s), 3.99 (3H, s), 7.34 (1H, d, J=7.5Hz), 7.56 (1H, s), 8.18 (1H, dd, J=7.5, 1Hz), 8.51 (1H, d, J=1Hz)

MASS (m/z) : 321 (M⁺+1)

BAD ORIGINAL

- 78 -

Preparation 33

A solution of methyl 4-(1-dimethylaminomethylene-2-oxopentyl)-3-nitrobenzoate (172 mg) in dioxane (9 ml) was refluxed for 4 days. The resulting mixture was evaporated in vacuo, and the residue was purified by thin layer chromatography with a mixture of hexane and ethyl acetate (2:1) to give methyl 3-nitro-4-(2-oxopentyl)benzoate (127 mg).

NMR (CDCl₃, δ) : 0.97 (3H, t, J=7Hz), 1.69 (2H, m),
2.60 (2H, t, J=7Hz), 3.95 (3H, s), 4.16 (2H, s),
7.36 (1H, d, J=8Hz), 8.22 (1H, d, J=8Hz), 8.73 (1H, s)

Preparation 34

To a solution of methyl 3-nitro-4-(2-oxopentyl)benzoate (114 mg) in a mixture of tetrahydrofuran (1.5 ml), ethanol (1.5 ml) and water (2.1 ml) was added sodium hydrosulfite (3.0 g), and the mixture was stirred under reflux for 30 minutes. The resulting mixture was evaporated in vacuo, and the residue was diluted with ethyl acetate. The organic phase was washed with water and brine, dried over sodium sulfate and evaporated in vacuo. The residue was purified by thin layer chromatography with a mixture of hexane and ethyl acetate (2:1) to give methyl 2-propylindole-6-carboxylate (54.6 mg).

Preparation 35

To a stirred solution of 3-isobutyryl-2-propylindole-6-carboxylic acid (331 mg) in tetrahydrofuran (5 ml) were added benzylalcohol (1.25 ml), dicyclohexylcarbodiimide (303 mg) and 4-dimethylaminopyridine (20 mg) at 20°C. The reaction mixture was stirred at 20°C for 8 hours. The precipitated urea was filtered off and the filtrate was evaporated in vacuo. The residue was extracted with ethyl acetate and the extract was washed with water two times and brine. The

- 79 -

organic phase was dried over sodium sulfate and evaporated in vacuo. The residue was chromatographed on silica gel eluting with a mixture of ethyl acetate and hexane (1:4) to give the crystals which were recrystallized from a mixture of ethyl acetate and hexane to give benzyl 3-isobutyryl-2-propylindole-6-carboxylate (215 mg) as colorless crystals.

mp : 102-104°C

IR (KBr) : 1700, 1655 cm^{-1}

NMR (CDCl_3 , δ) : 1.05 (3H, t, $J=7\text{Hz}$), 1.28 (6H, t, $J=7\text{Hz}$), 1.73-1.87 (2H, m), 3.17 (2H, t, $J=7\text{Hz}$), 3.45-3.53 (1H, m), 5.40 (2H, s), 7.32-7.50 (5H, m), 7.95 (2H, AB, $J=9$, 8Hz), 8.14 (1H, s), 8.59 (1H, br s)

MASS (m/z) : 364 (M^++1), 76 (bp)

Preparation 36

The following compound was prepared in a similar manner to that of Example 32.

Methyl 3-formylindole-6-carboxylate

NMR (CDCl_3 , δ) : 3.88 (3H, s), 7.83 (1H, dd, $J=1$, 8Hz), 8.12 (1H, s), 8.16 (1H, d, $J=8\text{Hz}$), 8.49 (1H, s), 12.45 (1H, br s)

Preparation 37

To a solution of methyl 3-isobutyryl-2-propylindole-6-carboxylate (201 mg) in carbon tetrachloride (7 ml) was added N-bromosuccinimide (167 mg) and 2,2'-azobis(4-methoxy-2,4-dimethylvaleronitrile) (20 mg) and refluxed for 30 minutes. The resulting mixture was filtered and the filtrate was evaporated in vacuo. The residue was purified by preparative thin layer chromatography on silica gel eluting with a mixture of hexane and ethyl acetate (2:1) to give methyl 2-(1-bromopropyl)-3-isobutyrylindole-6-carboxylate (179 mg).

- 80 -

This compound was used immediately without purification.

Preparation 38

To a solution of methyl 2-(1-bromopropyl)-3-isobutyrylindole-6-carboxylate (179 mg) in 1,2-dichloroethane (8 ml) was added N,N-diisopropylethylamine (0.24 ml) and refluxed for 40 minutes. The resulting mixture was evaporated in vacuo, then the residue was diluted with ethyl acetate and washed with diluted hydrochloric acid, water and brine. The organic phase was dried over sodium sulfate and evaporated in vacuo. Trituration with diethyl ether gave methyl 3-isobutyryl-2-(1-propenyl)indole-6-carboxylate (55.2 mg).

NMR (CDCl₃, δ) : 1.27 (6H, d, J=7Hz), 2.01 (3H, d, J=7Hz), 3.47 (1H, m), 3.93 (3H, s), 6.44 (1H, m), 7.32 (1H, d, J=16Hz), 7.89 (1H, d, J=8Hz), 7.94 (1H, d, J=8Hz), 8.11 (1H, s), 8.94 (1H, br s)

Preparation 39

To a solution of methyl 2-(1-bromopropyl)-3-isobutyrylindole-6-carboxylate (323 mg) in acetic acid (3 ml) was added potassium acetate (345 mg) and the mixture was stirred at 60°C for 2 hours. The resulting mixture was evaporated in vacuo, then the residue was diluted with ethyl acetate and washed with water, aqueous sodium bicarbonate and brine. The organic phase was dried over sodium sulfate and evaporated in vacuo. The residue was purified by preparative thin layer chromatography on silica gel eluting with a mixture of hexane and ethyl acetate (2:1) to give methyl 2-(1-acetoxypentyl)-3-isobutyrylindole-6-carboxylate (207 mg).

NMR (CDCl₃, δ) : 0.99 (3H, t, J=7Hz), 1.23 (3H, d, J=7Hz), 1.29 (3H, d, J=7Hz), 1.94 (1H, m), 2.08 (1H, m), 2.18 (3H, s), 3.52 (1H, m), 3.94 (3H, s), 6.67 (1H, m), 7.88 (1H, d, J=8Hz), 7.94 (1H, d, J=8Hz), 8.16 (1H, s), 9.09 (1H, br s)

BAD ORIGINAL

- 81 -

Preparation 40

To a mixture of methyl 2-propylindole-6-carboxylate (10 g), methoxyacetic acid (4.6 ml) and carbontetrachloride (13.4 ml) in 1,2-dichloroethane (45 ml) was added slowly
5 triphenylphosphine (16.7 g) in 1,2-dichloroethane (30 ml) over 1 hour under reflux, and the resulting mixture was heated under reflux for additional 8 hours. After evaporation of solvent, the residue was chromatographed on silica gel eluting with a mixture of hexane and ethyl acetate
10 (1:1) and triturated with diethyl ether to give methyl 3-methoxyacetyl-2-propylindole-6-carboxylate (8.11 g).

Preparation 41

The following compound was prepared in a similar manner
15 to that of Preparation 15 (1).

Methyl 3-ethoxyacetyl-2-propylindole-6-carboxylate

NMR (CDCl₃, δ) : 1.05 (3H, t, J=7Hz), 1.32 (3H, t, J=7Hz), 1.84 (2H, sextet, J=8Hz), 3.22 (2H, t, J=7Hz), 3.74 (3H, q, J=7Hz), 3.97 (3H, s), 4.75
20 (2H, s), 7.83 (1H, d, J=8Hz), 7.94 (1H, d, J=8Hz), 8.15 (1H, s), 9.27 (1H, br s)

Preparation 42

To a stirred mixture of methyl 4-hydroxyphenylacetate (10.0 g) in acetic acid (55 ml) was added nitric acid (22.1 ml) at 0°C. The reaction mixture was stirred at 0°C for 2 hours. After warmed to 20°C, the reaction mixture was diluted with water (200 ml) and precipitated crystals were
30 collected. The crystals were dissolved in chloroform, and the solution was washed with water, dried over magnesium sulfate and evaporated in vacuo. The residue was recrystallized from a mixture of chloroform and hexane to give methyl 4-hydroxy-3-nitrophenylacetate (9.3 g) as yellow
35 crystals.

- 82 -

mp : 64-69°C

IR (KBr) : 1734, 1540, 1534, 1263, 1170 cm^{-1} NMR (CDCl_3 , δ) : 3.64 (2H, s), 3.73 (3H, s), 7.14 (1H, d, $J=8\text{Hz}$), 7.52 (1H, dd, $J=8, 1\text{Hz}$), 8.02 (1H, d, $J=1\text{Hz}$)MASS (m/z) : 210 (M^+-1)Preparation 43

Iron powder (2.5 g) was added to a stirred mixture of methyl 3-nitro-4-trifluoromethanesulfonyloxyphenylacetate (2.97 g) and conc. hydrochloric acid (7.3 ml) in methanol (22 ml) at 0°C in some small portion. The reaction mixture was stirred at 20°C for 2 hours, then poured into a mixture of ethyl acetate and saturated sodium bicarbonate. The organic phase was washed with saturated sodium bicarbonate and brine, dried over sodium sulfate and evaporated in vacuo. The residue was chromatographed on silica gel eluting with a mixture of ethyl acetate and hexane (1:4) to give methyl 3-amino-4-trifluoromethanesulfonyloxyphenylacetate (2.34 g) as colorless crystals.

mp : 66-69°C

NMR (CDCl_3 , δ) : 3.57 (2H, s), 3.71 (3H, s), 3.94 (2H, s), 6.67 (1H, dd, $J=7.5, 1\text{Hz}$), 6.79 (1H, d, $J=1\text{Hz}$), 7.11 (1H, d, $J=7.5\text{Hz}$)Preparation 44

The following compounds were prepared from methyl 1-acetyl-2-propylindol-6-ylacetate in a similar manner to that of Preparation 26.

Methyl 2-propylindol-6-ylacetate

IR (Neat) : 3400, 1740 cm^{-1} NMR (CDCl_3 , δ) : 1.00 (3H, t, $J=7\text{Hz}$), 1.75 (2H, sextet, $J=7\text{Hz}$), 2.72 (2H, t, $J=7\text{Hz}$), 3.70 (3H, s), 3.72 (2H, s), 6.22 (1H, s), 6.99 (1H, d, $J=7.5\text{Hz}$),

- 83 -

7.22 (1H, s), 7.47 (1H, d, J=7.5Hz), 7.83 (1H, br s)

MASS (m/z) : 232 (M^+ +1), 74 (bp)

5 Ethyl 2-propylindol-6-ylacetate

IR (Neat) : 3400, 1735 cm^{-1}

NMR (CDCl_3 , δ) : 1.00 (3H, t, J=7Hz), 1.05 (3H, t, J=7Hz), 1.74 (2H, sextet, J=7Hz), 2.72 (2H, t, J=7Hz), 3.69 (3H, s), 4.13 (2H, q, J=7Hz), 6.20 (1H, s), 6.99 (1H, d, J=7.5Hz), 7.23 (1H, s), 7.46 (1H, d, J=7.5Hz), 7.83 (1H, br s)

MASS (m/z) : 346 (M^+ +1), 74 (bp)

2-Propylindol-6-ylacetic acid

15 mp : 85-87°C

IR (KBr) : 3381, 1701, 1691 cm^{-1}

NMR (CDCl_3 , δ) : 1.00 (3H, t, J=7Hz), 1.73 (2H, sextet, J=7Hz), 2.72 (2H, t, J=7Hz), 3.73 (2H, s), 6.21 (1H, s), 6.98 (1H, d, J=7.5Hz), 7.21 (1H, s), 7.46 (1H, d, J=7.5Hz), 7.83 (1H, br s)

MASS (m/z) : 216 (M^+ -1, bp)

Preparation 45

To a stirred solution of methyl 3-ethylindole-6-carboxylate (138 mg) in dichloromethane (5 ml) was added sulfuryl chloride (0.066 ml), and the mixture was stirred at 20°C for 1 hour. The resulting mixture was poured into ice and extracted with ethyl acetate. The combined organic phase was washed with aqueous sodium bicarbonate and brine, then dried over sodium sulfate and evaporated in vacuo. The residue was chromatographed on silica gel eluting with a mixture of hexane and ethyl acetate (4:1) to give methyl 2-chloro-3-ethylindole-6-carboxylate (58.2 mg) as a solid.

35 NMR (CDCl_3 , δ) : 1.26 (3H, t, J=7Hz), 2.76 (2H, q, J=7Hz), 3.92 (3H, s), 7.54 (1H, d, J=8Hz), 7.82

- 84 -

(1H, d, J=8Hz) 8.02 (1H, s), 8.19 (1H, br s)

Preparation 46

To a stirred solution of methyl 3-formylindole-6-carboxylate (368 mg) in 1,4-dioxane (10 ml) was added acetylmethylene triphenylphosphorane (1.15 g), and the mixture was stirred under reflux for 12 hours. The resulting mixture was evaporated in vacuo, redissolved with ethyl acetate and washed with 1N hydrochloric acid and brine. The organic phase was dried over sodium sulfate and evaporated in vacuo. The residue was chromatographed on silica gel eluting with a mixture of chloroform and ethyl acetate (1:2) to give methyl 3-(3-oxo-1-butenyl)indole-6-carboxylate (75 mg) as a solid.

NMR (CDCl₃, δ) : 2.39 (3H, s), 3.95 (3H, s), 6.79 (1H, d, J=15Hz), 7.71 (1H, s), 7.80 (1H, d, J=8Hz), 7.87-7.96 (2H, m), 8.14 (1H, s)

Preparation 47

The following compound was prepared from in a similar manner to that of Preparation 46.

Methyl 3-(2-methoxycarbonylethenyl)indole-6-carboxylate

NMR (DMSO-d₆, δ) : 3.72 (3H, s), 4.87 (3H, s), 6.44 (1H, d, J=15Hz), 7.76 (1H, d, J=8Hz), 7.89 (1H, d, J=15Hz), 7.98 (1H, d, J=8Hz), 8.10 (1H, s), 8.20 (1H, s)

Preparation 48

To a solution of methyl 3-(2-methoxycarbonylethenyl)indole-6-carboxylate (213 mg) in a mixture of 1,4-dioxane (2 ml) and methanol (3 ml) was added 10% palladium on carbon (40 mg) and the mixture was stirred under hydrogen at 20°C for 6.5 hours. The resulting mixture was filtered through celite and the filtrate was evaporated in vacuo. The residue was

- 85 -

trituated with diisopropyl ether to give methyl 3-(2-methoxycarbonylethyl)indole-6-carboxylate (177 mg).

5 NMR (CDCl₃, δ) : 2.72 (2H, t, J=7Hz), 3.12 (2H, t, J=7Hz), 3.68 (3H, s), 3.94 (3H, s), 7.20 (1H, d, J=2Hz), 7.62 (1H, d, J=8Hz), 7.82 (1H, d, J=8Hz), 8.12 (1H, s), 8.21 (1H, br s)

Preparation 49

10 The following compound was prepared from a similar manner to that of Preparation 30.

3-(6-Methoxycarbonylindol-3-yl)propionic acid

15 NMR (CDCl₃, δ) : 2.72 (2H, t, J=7Hz), 3.10 (2H, t, J=7Hz), 3.94 (3H, s), 7.19 (1H, s), 7.60 (1H, d, J=8Hz), 7.77 (1H, d, J=8Hz), 8.10 (1H, s)

Preparation 50

The following compound was prepared in a similar manner to that of Preparation 31.

20

Methyl 3-oxo-1,2,3,4-tetrahydrocyclopent[b]indole-6-carboxylate

25 NMR (CDCl₃, δ) : 3.05 (2H, m), 3.14 (2H, m), 3.97 (3H, s), 7.76 (1H, d, J=8Hz), 7.85 (1H, d, J=8Hz), 8.21 (1H, s)

Preparation 51

The following compounds described in (1) to (6) were prepared in a similar manner to that of Preparation 8 (1).

30

(1) 3-Cyclopropanecarbonyl-2-propylindole-6-carboxylic acid

mp : 250.5-251.5°C (dec.)

IR (KBr) : 1685, 1600, 1463, 1424, 1300 cm⁻¹

35 NMR (CDCl₃-CD₃OD, δ) : 1.00-1.09 (2H, m), 1.02 (3H, t, J=7Hz), 1.25-1.29 (2H, m), 1.81 (2H, sextet,



- 86 -

J=7Hz), 2.59-2.69 (1H, m), 3.12 (2H, t, J=7Hz),
7.99 (2H, AB, J=7.5, 7.5Hz), 8.09 (1H, s)
MASS (m/z) : 270 (M^+-1)

5 (2) 3-Cyclobutanecarbonyl-2-propylindole-6-carboxylic acid
mp : 244-245°C
IR (KBr) : 1682, 1419, 1292 cm^{-1}
NMR (CDCl_3 - CD_3OD , δ) : 1.05 (3H, t, J=7Hz), 1.80 (2H,
sextet, J=7Hz), 1.92-2.15 (2H, m), 2.29-2.49 (2H,
10 m), 4.01 (1H, quintet, J=7Hz), 7.90 (2H, s), 8.08
(1H, s)
MASS (m/z) : 286 (M^++1), 74 (bp)

(3) 3-Cyclopentanecarbonyl-2-propylindole-6-carboxylic acid
15 mp : 233-235°C
IR (KBr) : 1673, 1611, 1463, 1453 cm^{-1}
NMR (CDCl_3 - CD_3OD , δ) : 0.99 (3H, t, J=7Hz), 1.51-1.79
(6H, m), 1.89-1.97 (4H, m), 3.10 (2H, t, J=7Hz),
3.70 (1H, quintet, J=7Hz), 7.85-7.94 (2H, m), 8.05
20 (1H, s)
MASS (m/z) : 298 (M^+-1 , bp)

(4) 3-Cyclohexanecarbonyl-2-propylindole-6-carboxylic acid
mp : 217-218°C
25 IR (KBr) : 1675, 1614, 1457 cm^{-1}
NMR (CDCl_3 - CD_3OD , δ) : 0.99 (3H, t, J=7Hz), 1.19-1.56
(6H, m), 1.74 (2H, sextet, J=7Hz), 1.80-1.95 (4H,
m), 3.08 (2H, t, J=7Hz), 3.09-3.20 (1H, m), 7.80
(1H, d, J=8Hz), 7.88 (1H, dd, J=8, 1Hz), 8.03 (1H,
30 d, J=1Hz)
MASS (m/z) : 312 (M^+-1 , bp)

(5) 3-(3-Methyl-2-butenoyl)-2-propylindole-6-carboxylic acid
mp : 246-248°C (dec.)
35 IR (KBr) : 1669, 1465, 1423 cm^{-1}

BAD ORIGINAL

- 87 -

NMR (DMSO- d_6 , δ) : 0.96 (3H, t, $J=7\text{Hz}$), 1.75 (2H, sextet, $J=7\text{Hz}$), 2.00 (3H, s), 2.09 (3H, s), 3.08 (2H, t, $J=7\text{Hz}$), 6.60 (1H, s), 7.73 (1H, d, $J=7.5\text{Hz}$), 7.95 (1H, d, $J=7.5\text{Hz}$), 7.99 (1H, s)

5 MASS (m/z) : 284 (M^+-1 , bp), 82 (bp)

Preparation 52

The following compounds described in (1) to (6) were prepared in the similar manner to that of Example 6.

10

(1) 3-Cyclopropanecarbonyl-2-propylindole-6-carboxamide

mp : 120-122°C

IR (KBr) : 1670, 1623, 1598, 1394 cm^{-1}

15 NMR (DMSO- d_6 , δ) : 0.94 (3H, t, $J=7\text{Hz}$), 0.99-1.04 (4H, m), 1.73 (2H, sextet, $J=7\text{Hz}$), 2.55-2.62 (1H, m), 3.07 (2H, t, $J=7\text{Hz}$), 7.22 (1H, br s), 7.69 (1H, dd, $J=7.5$, 1Hz), 7.93 (1H, d, $J=1\text{Hz}$), 7.96 (1H, br s), 8.00 (1H, d, $J=7.5\text{Hz}$)

MASS (m/z) : 269 (M^+-1), 98 (bp)

20

(2) 3-Cyclobutanecarbonyl-2-propylindole-6-carboxamide

mp : 253-255°C

IR (KBr) : 1675, 1624, 1605, 1456, 1397 cm^{-1}

25 NMR (DMSO- d_6 , δ) : 0.97 (3H, t, $J=7\text{Hz}$), 1.66-1.89 (3H, m), 1.97-2.09 (1H, m), 2.23-2.30 (4H, m), 3.09 (2H, t, $J=7\text{Hz}$), 3.99 (1H, quintet, $J=7\text{Hz}$), 7.24 (1H, br s), 7.69 (1H, d, $J=7.5\text{Hz}$), 7.86 (1H, d, $J=7.5\text{Hz}$), 7.90 (1H, s), 7.97 (1H, br s)

MASS (m/z) : 285 (M^++1), 85 (bp)

30

(3) 3-Cyclopentanecarbonyl-2-propylindole-6-carboxamide

mp : 213-215°C

IR (KBr) : 1666, 1628, 1623, 1604 cm^{-1}

35 NMR (CDCl_3 - CD_3OD , δ) : 1.01 (3H, t, $J=7\text{Hz}$), 1.61-1.83 (6H, m), 1.90-1.98 (4H, m), 3.13 (2H, t, $J=7\text{Hz}$),

BAD ORIGINAL

- 88 -

3.69 (1H, quintet, J=7Hz), 7.52 (1H, dd, J=8, 1Hz),
7.91 (1H, d, J=1Hz), 7.96 (1H, d, J=8Hz)

MASS (m/z) : 299 (M^+ +1), 74 (bp)

5 (4) 3-Cyclohexanecarbonyl-2-propylindole-6-carboxamide

mp : 245-247°C

IR (KBr) : 1663, 1627, 1595, 1459, 1402 cm^{-1}

10 NMR (DMSO- d_6 , δ) : 0.95 (3H, t, J=7Hz), 1.16-1.30 (1H, m), 1.35-1.46 (4H, m), 1.70 (2H, sextet, J=7Hz),
1.75-1.88 (5H, m), 3.05 (2H, t, J=7Hz), 3.10-3.17 (1H, m), 7.25 (1H, br s), 7.70 (1H, dd, J=7.5, 1Hz), 7.81 (1H, d, J=7.5Hz), 7.93 (1H, d, J=1Hz), 7.95 (1H, br s)

MASS (m/z) : 313 (M^+ +1), 85 (bp)

15

(5) 3-(3-Methyl-2-butenoyl)-2-propylindole-6-carboxamide

mp : 179-181°C

IR (KBr) : 1669, 1648, 1591, 1458, 1394 cm^{-1}

20 NMR (DMSO- d_6 , δ) : 0.95 (3H, t, J=7Hz), 1.72 (2H, sextet, J=7Hz), 1.99 (3H, s), 2.05 (3H, s), 3.05 (2H, t, J=7Hz), 6.59 (1H, s), 7.22 (1H, br s), 7.67 (1H, d, J=7.5Hz), 7.88 (1H, d, J=7.5Hz), 7.90 (1H, s), 7.92 (1H, br s)

MASS (m/z) : 285 (M^+ +1), 85 (bp)

25

(6) 3-(3-Methoxybutanoyl)-2-propylindole-6-carboxamide

mp : 140-144°C

IR (KBr) : 1644, 1623, 1604, 1460, 1394 cm^{-1}

30 NMR (CDCl_3 , δ) : 1.02 (3H, t, J=7Hz), 1.30 (3H, d, J=7Hz), 1.80 (2H, sextet, J=7Hz), 2.98 (1H, dd, J=15, 7Hz), 3.17 (2H, t, J=7Hz), 3.39 (1H, dd, J=15, 7Hz), 3.40 (3H, s), 7.10 (1H, sextet, J=7Hz), 7.55 (1H, dd, J=8, 1Hz), 8.02 (1H, d, J=8Hz), 8.10 (1H, d, J=1Hz), 9.60 (1H, br s)

35 MASS (m/z) : 303 (M^+ +1), 74 (bp)

- 89 -

Preparation 53

The following compound was prepared from methyl 3-crotonyl-2-propylindole-6-carboxylate in a similar manner to that of Preparation 8 (1).

5

3-(3-Methoxybutanoyl)-2-propylindole-6-carboxylic acid

mp : 286-288°C (dec.)

IR (KBr) : 3288, 1685, 1645, 1620 cm^{-1}

10 NMR (DMSO- d_6 , δ) : 0.96 (3H, t, J=7Hz), 1.19 (3H, d, J=7Hz), 1.73 (2H, sextet, J=7Hz), 2.90 (1H, dd, J=15, 7Hz), 3.08 (2H, t, J=7Hz), 3.13 (3H, s), 3.15 (1H, dd, J=15, 7Hz), 3.91 (1H, sextet, J=7Hz), 7.26 (1H, d, J=8Hz), 7.99 (1H, s), 8.00 (1H, d, J=8Hz)

15 MASS (m/z) : 302 (M^+-1), 98 (bp)

15

20

25

30

35

- 90 -

Example 1

To a solution of methyl 3-acetyl-2-propylindole-6-carboxylate (74 mg) in dimethylformamide (1.4 ml) was added sodium hydride (60%, 15.4 mg). The mixture was stirred at 20°C for 30 minutes, then 2-chlorobenzyl bromide (0.045 ml) was added. After stirred for 1 hour, the mixture was diluted with ethyl acetate and washed with water and brine. The organic phase was dried over sodium sulfate and evaporated in vacuo to give methyl 3-acetyl-1-(2-chlorobenzyl)-2-propylindole-6-carboxylate (125 mg) as solid.

NMR (CDCl₃, δ) : 1.01 (3H, t, J=7Hz), 1.63 (2H, m), 2.74 (3H, s), 3.05 (2H, m), 3.89 (3H, s), 5.49 (2H, s), 6.22 (1H, d, J=8Hz), 7.03 (1H, t, J=8Hz), 7.20 (1H, t, J=8Hz), 7.46 (1H, d, J=8Hz), 7.93 (1H, s), 7.97 (1H, d, J=8Hz), 8.04 (1H, d, J=8Hz)

Example 2

To a solution of methyl 3-acetyl-1-(2-chlorobenzyl)-2-propylindole-6-carboxylate (125 mg) in ethanol (6 ml) was added 1N aqueous sodium hydroxide (0.7 ml), and the mixture was stirred under reflux for 1 hour. The resulting mixture was evaporated in vacuo, and the residue was acidified with 1N hydrochloric acid (0.75 ml) and extracted with ethyl acetate. The extract was washed with brine, dried over sodium sulfate and evaporated in vacuo. The residue was triturated with isopropyl ether to give 3-acetyl-1-(2-chlorobenzyl)-2-propylindole-6-carboxylic acid (78 mg) as solid.

NMR (CDCl₃, δ) : 1.02 (3H, t, J=7Hz), 1.61 (2H, m), 2.76 (3H, s), 3.08 (2H, m), 5.52 (2H, s), 6.24 (1H, d, J=8Hz), 7.04 (1H, t, J=8Hz), 7.22 (1H, t, J=8Hz), 7.46 (1H, d, J=8Hz), 7.99 (1H, s), 8.03 (1H, d, J=8Hz), 8.06 (1H, d, J=8Hz)

Example 3

BAD ORIGINAL

- 91 -

To a solution of 3-acetyl-1-(2-chlorobenzyl)-2-propylindole-6-carboxylic acid (74 mg) in dimethylformamide (2 ml) were added 1-hydroxybenzotriazole (38 mg), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (98 mg) and 3N methanol solution of ammonia (0.5 ml). After stirred at 20°C for 14 hours, the resulting mixture was diluted with ethyl acetate. The organic phase was washed successively with 1N hydrochloric acid, water, aqueous sodium bicarbonate and brine, dried over sodium sulfate and evaporated in vacuo. The residue was triturated with isopropyl ether to give 3-acetyl-1-(2-chlorobenzyl)-2-propylindole-6-carboxamide (67 mg) as colorless crystals.

mp : 208-211°C

NMR (CDCl₃, δ) : 1.01 (3H, t, J=7Hz), 1.61 (2H, m), 2.73 (3H, s), 3.06 (2H, m), 5.49 (2H, s), 6.22 (1H, dd, J=1, 8Hz), 7.02 (1H, dt, J=1, 8Hz), 7.21 (1H, dt, J=1, 8Hz), 7.45 (1H, dd, J=1, 8Hz), 7.63 (1H, dd, J=1, 8Hz), 7.84 (1H, d, J=8Hz), 8.07 (1H, d, J=8Hz)

20

Example 4

Methyl 1-(2-chlorobenzyl)-3-isobutyryl-2-propylindole-6-carboxylate (533 mg) was prepared from methyl 3-isobutyryl-2-propylindole-6-carboxylate (440 mg) and 2-chlorobenzyl bromide (346 mg) in a similar manner to that of Example 1.

NMR (CDCl₃, δ) : 1.01 (3H, t, J=8Hz), 1.30 (6H, d, J=8Hz), 1.55-1.66 (2H, m), 3.02-3.07 (2H, m), 3.58 (2H, septet, J=8Hz), 3.90 (3H, s), 5.50 (2H, s), 6.24 (1H, dd, J=1, 8Hz), 7.05 (1H, dt, J=1, 8Hz), 7.24 (1H, dt, J=1, 8Hz), 7.46 (1H, dd, J=1, 8Hz), 7.95 (1H, s), 7.97 (2H, s)

30

Example 5

1-(2-Chlorobenzyl)-3-isobutyryl-2-propylindole-6-carboxylic acid (450 mg) was prepared from methyl 1-(2-

35

BAD ORIGINAL



- 92 -

chlorobenzyl)-3-isobutyryl-2-propylindole-6-carboxylate (510 mg) in a similar manner to that of Example 2.

5 NMR (DMSO-d₆, δ) : 0.92 (3H, t, J=8Hz), 1.18 (6H, d, J=8Hz), 1.36-1.52 (2H, m), 3.02-3.08 (2H, m), 3.55 (2H, septet, J=8Hz), 5.68 (2H, s), 6.28 (1H, dd, J=1, 8Hz), 7.18 (1H, dt, J=1, 8Hz), 7.32 (1H, dt, J=1, 8Hz), 7.52 (1H, dd, J=1, 8Hz), 7.84 (1H, dd, J=1, 8Hz), 7.97 (1H, d, J=1Hz), 8.00 (1H, d, J=8Hz)

10 Example 6

To a solution of 1-(2-chlorobenzyl)-3-isobutyryl-2-propylindole-6-carboxylic acid (150 mg) in dimethylformamide (3 ml) were added 1-hydroxybenzotriazole (102 mg), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (109 mg). After stirred at 20°C over night, the resulting mixture was poured into 28% aqueous ammonia (5 ml). The mixture was partitioned between ethyl acetate and water, and the organic phase was washed with 1N hydrochloric acid and brine, dried over sodium sulfate and evaporated in vacuo. The crystalline residue was recrystallized from a mixture of ethyl acetate and hexane to give 1-(2-chlorobenzyl)-3-isobutyryl-2-propylindole-6-carboxamide (123 mg) as colorless crystals.

mp : 185-186°C

25 NMR (CDCl₃, δ) : 1.01 (3H, t, J=8Hz), 1.30 (6H, d, J=8Hz), 1.55-1.66 (2H, m), 3.00-3.06 (2H, m), 3.56 (2H, septet, J=8Hz), 5.49 (2H, s), 6.24 (1H, dd, J=1, 8Hz), 7.04 (1H, dt, J=1, 8Hz), 7.23 (1H, dt, J=1, 8Hz), 7.46 (1H, dd, J=1, 8Hz), 7.63 (1H, dd, J=1, 8Hz), 7.85 (1H, d, J=1Hz), 7.97 (1H, d, J=8Hz)

30

Example 7

Methyl 1-(2-chlorobenzyl)-3-propionyl-2-propylindole-6-carboxylate (436 mg) was prepared from methyl 3-propionyl-2-propylindole-6-carboxylate (260 mg) and 2-chlorobenzyl bromide (215 mg) in a similar manner to that of Example 1.

BAD ORIGINAL

- 93 -

NMR (CDCl₃, δ) : 1.02 (3H, t, J=8Hz), 1.30 (3H, t, J=8Hz), 1.55-1.68 (2H, m), 3.00-3.16 (4H, m), 3.90 (3H, s), 5.49 (2H, s), 6.22 (1H, dd, J=1, 8Hz), 7.05 (1H, dt, J=1, 8Hz), 7.23 (1H, dt, J=1, 8Hz), 7.46 (1H, dd, J=1, 8Hz), 7.93 (1H, d, J=8Hz), 7.96 (1H, dd, J=1, 8Hz), 8.03 (1H, d, J=8Hz)

Example 8

1-(2-Chlorobenzyl)-3-propionyl-2-propylindole-6-carboxylic acid (308 mg) was prepared from methyl 1-(2-chlorobenzyl)-3-propionyl-2-propylindole-6-carboxylate (425 mg) in a similar manner to that of Example 2.

NMR (DMSO-d₆, δ) : 0.94 (3H, t, J=8Hz), 1.14 (3H, t, J=8Hz), 1.49 (2H, sextet, J=8Hz), 3.00-3.10 (4H, m), 5.67 (2H, s), 6.27 (1H, dd, J=1, 8Hz), 7.18 (1H, dt, J=1, 8Hz), 7.32 (1H, dt, J=1, 8Hz), 7.56 (1H, dd, J=1, 8Hz), 7.83 (1H, dd, J=1, 8Hz), 7.96 (1H, d, J=1Hz), 8.09 (1H, d, J=8Hz)

Example 9

1-(2-Chlorobenzyl)-3-propionyl-2-propylindole-6-carboxamide (81 mg) was prepared from 1-(2-chlorobenzyl)-3-propionyl-2-propylindole-6-carboxylic acid (100 mg) in a similar manner to that of Example 6.

mp : 151-152°C

NMR (CDCl₃, δ) : 1.02 (3H, t, J=8Hz), 1.30 (3H, t, J=8Hz), 1.62 (2H, sextet, J=8Hz), 3.04-3.14 (4H, m), 5.50 (2H, s), 6.22 (1H, dd, J=1, 8Hz), 7.03 (1H, dt, J=1, 8Hz), 7.22 (1H, dt, J=1, 8Hz), 7.45 (1H, dd, J=1, 8Hz), 7.64 (1H, dd, J=1, 8Hz), 7.84 (1H, d, J=1Hz), 8.06 (1H, d, J=8Hz)

Example 10

Methyl 1-(2-chlorobenzyl)-2-isobutyl-3-isobutyrylindole-6-carboxylate (258 mg) was prepared from methyl 2-isobutyl-3-

- 94 -

isobutyrylindole-6-carboxylate (210 mg) and 2-chlorobenzyl bromide (157 mg) in a similar manner to that of Example 1.

5 NMR (CDCl₃, δ) : 0.97 (6H, d, J=7Hz), 1.31 (6H, d, J=7Hz), 1.96-2.10 (1H, m), 3.04 (2H, d, J=7Hz), 3.60 (1H, septet, J=7Hz), 3.90 (3H, s), 5.53 (2H, s), 6.18 (1H, d, J=8Hz), 7.04 (1H, t, J=8Hz), 7.23 (1H, t, J=8Hz), 7.46 (1H, t, J=8Hz), 7.94 (1H, s), 7.96 (2H, s)

10 Example 11

1-(2-Chlorobenzyl)-2-isobutyl-3-isobutyrylindole-6-carboxylic acid (184 mg) was prepared from methyl 1-(2-chlorobenzyl)-2-isobutyl-3-isobutyrylindole-6-carboxylate (213 mg) in a similar manner to that of Example 2.

15 NMR (DMSO-d₆, δ) : 0.88 (6H, d, J=8Hz), 1.17 (6H, d, J=7Hz), 1.82-1.95 (1H, m), 3.07 (2H, d, J=8Hz), 3.57 (1H, septet, J=7Hz), 5.68 (2H, s), 6.25 (1H, d, J=8Hz), 7.18 (1H, t, J=8Hz), 7.33 (1H, t, J=8Hz), 7.57 (1H, d, J=8Hz), 7.85 (1H, d, J=8Hz),
20 7.95 (1H, s), 8.00 (1H, d, J=8Hz)

Example 12

1-(2-Chlorobenzyl)-2-isobutyl-3-isobutyrylindole-6-carboxamide (143 mg) was prepared from 1-(2-chlorobenzyl)-2-isobutyl-3-isobutyrylindole-6-carboxylic acid (160 mg) in a similar manner to that of Example 6.

30 NMR (DMSO-d₆, δ) : 0.86 (6H, d, J=8Hz), 1.17 (6H, d, J=7Hz), 1.80-1.94 (1H, m), 3.02 (2H, d, J=8Hz), 3.57 (1H, septet, J=7Hz), 5.62 (2H, s), 6.16 (1H, d, J=8Hz), 7.18 (1H, t, J=8Hz), 7.30-7.35 (2H, m), 7.57 (1H, d, J=8Hz), 7.82 (1H, d, J=8Hz), 7.94 (1H, s), 7.96 (1H, d, J=8Hz), 8.00 (1H, s)

Example 13

35 Methyl 1-(2-chlorobenzyl)-2-ethyl-3-propionylindole-6-

BAD ORIGINAL

- 95 -

carboxylate (278 mg) was prepared from methyl 2-ethyl-3-propionylindole-6-carboxylate (215 mg) and 2-chlorobenzyl bromide (0.24 ml) in a similar manner to that of Example 1.

5 NMR (CDCl₃, δ) : 1.22 (3H, t, J=7Hz), 1.30 (3H, t, J=7Hz), 3.05-3.20 (4H, m), 3.90 (3H, s), 5.50 (2H, s), 6.22 (1H, d, J=8Hz), 7.02 (1H, t, J=8Hz), 7.20 (1H, t, J=8Hz), 7.46 (1H, d, J=8Hz), 7.92 (1H, s), 7.95 (1H, d, J=8Hz), 8.04 (1H, d, J=8Hz)

10 Example 14

1-(2-Chlorobenzyl)-2-ethyl-3-propionylindole-6-carboxylic acid (417 mg) was prepared from methyl 1-(2-chlorobenzyl)-2-ethyl-3-propionylindole-6-carboxylate (453 mg) in a similar manner to that of Example 2.

15 NMR (DMSO-d₆, δ) : 1.09 (3H, t, J=7Hz), 1.17 (3H, t, J=7Hz), 3.08 (2H, t, J=7Hz), 3.11 (2H, t, J=7Hz), 5.68 (2H, s), 6.24 (1H, d, J=8Hz), 7.18 (1H, t, J=8Hz), 7.31 (1H, t, J=8Hz), 7.57 (1H, d, J=8Hz), 7.83 (1H, d, J=8Hz), 7.95 (1H, s), 8.13 (1H, d, J=8Hz)
20

Example 15

1-(2-Chlorobenzyl)-2-ethyl-3-propionylindole-6-carboxamide (242 mg) was prepared from 1-(2-chlorobenzyl)-2-ethyl-3-propionylindole-6-carboxylic acid (252 mg) in a similar manner to that of Example 3.

25 NMR (CDCl₃, δ) : 1.23 (3H, t, J=7Hz), 1.29 (3H, t, J=7Hz), 3.08-3.18 (4H, m), 5.49 (2H, s), 6.19 (1H, d, J=8Hz), 7.02 (1H, t, J=8Hz), 7.21 (1H, t, J=8Hz), 7.46 (1H, d, J=8Hz), 7.62 (1H, d, J=8Hz), 7.83 (1H, s), 8.09 (1H, d, J=8Hz)
30

Example 16

35 Methyl 2-acetyl-1-(2-chlorobenzyl)-3-isobutylindole-6-carboxylate (71.4 mg) was prepared from methyl 2-acetyl-3-

BAD ORIGINAL

- 96 -

isobutylindole-6-carboxylate (58 mg) and 2-chlorobenzyl bromide (0.04 ml) in a similar manner to that of Example 1.

5 NMR (CDCl₃, δ) : 1.02 (6H, d, J=7Hz), 2.02 (1H, m),
2.59 (3H, s), 3.01 (2H, d, J=7Hz), 3.90 (3H, s),
5.84 (2H, s), 6.19 (1H, d, J=8Hz), 6.99 (1H, t,
J=8Hz), 7.15 (1H, t, J=8Hz), 7.40 (1H, d, J=8Hz),
7.75 (1H, d, J=8Hz), 7.83 (1H, d, J=8Hz), 7.98 (1H,
s)

10 Example 17

2-Acetyl-1-(2-chlorobenzyl)-3-isobutylindole-6-carboxylic acid (45.3 mg) was prepared from methyl 2-acetyl-1-(2-chlorobenzyl)-3-isobutylindole-6-carboxylate (67 mg) in a similar manner to that of Example 2.

15 NMR (CDCl₃, δ) : 1.02 (6H, d, J=7Hz), 2.03 (1H, m),
2.62 (3H, s), 3.03 (2H, d, J=7Hz), 5.76 (2H, s),
6.19 (1H, d, J=8Hz), 7.00 (1H, t, J=8Hz), 7.14 (1H,
t, J=8Hz), 7.41 (1H, d, J=8Hz), 7.77 (1H, d,
J=8Hz), 7.86 (1H, d, J=8Hz), 8.02 (1H, s)

20

Example 18

2-Acetyl-1-(2-chlorobenzyl)-3-isobutylindole-6-carboxamide (33.4 mg) was prepared from 2-acetyl-1-(2-chlorobenzyl)-3-isobutylindole-6-carboxylic acid (41.7 mg) in a similar manner to that of Example 3.

25 NMR (CDCl₃, δ) : 1.01 (6H, d, J=7Hz), 2.02 (1H, m),
2.62 (3H, s), 3.03 (2H, d, J=7Hz), 5.54 (2H, s),
6.22 (1H, d, J=8Hz), 6.99 (1H, t, J=8Hz), 7.16 (1H,
t, J=8Hz), 7.41 (1H, d, J=8Hz), 7.54 (1H, d,
30 J=8Hz), 7.78 (1H, d, J=8Hz), 7.79 (1H, s)

Example 19

Methyl 1-(2-chlorobenzyl)-3-ethyl-2-propionylindole-6-carboxylate (66 mg) was prepared from methyl 3-ethyl-2-propionylindole-6-carboxylate (88 mg) and 2-chlorobenzyl

35

- 97 -

bromide (0.051 ml) in a similar manner to that of Example 1.

NMR (CDCl₃, δ) : 1.16 (3H, t, J=7Hz), 1.38 (3H, t, J=7Hz), 2.95 (2H, q, J=7Hz), 3.14 (2H, q, J=7Hz), 3.90 (3H, s), 5.72 (2H, s), 6.23 (1H, d, J=8Hz), 6.98 (1H, t, J=8Hz), 7.14 (1H, t, J=8Hz), 7.39 (1H, d, J=8Hz), 7.77 (1H, d, J=8Hz), 7.85 (1H, d, J=8Hz), 7.97 (1H, s)

Example 20

10 1-(2-Chlorobenzyl)-3-ethyl-2-propionylindole-6-carboxylic acid (48.7 mg) was prepared from methyl 1-(2-chlorobenzyl)-3-ethyl-2-propionylindole-6-carboxylate (59.4 mg) in a similar manner to that of Example 2.

15 NMR (CDCl₃, δ) : 1.16 (3H, t, J=7Hz), 1.37 (3H, t, J=7Hz), 2.94 (2H, q, J=7Hz), 3.15 (2H, q, J=7Hz), 5.72 (2H, s), 6.25 (1H, d, J=8Hz), 6.99 (1H, t, J=8Hz), 7.15 (1H, t, J=8Hz), 7.40 (1H, d, J=8Hz), 7.78 (1H, d, J=8Hz), 7.87 (1H d, J=8Hz), 8.01 (1H, s)

20

Example 21

1-(2-Chlorobenzyl)-3-ethyl-2-propionylindole-6-carboxamide (40.4 mg) was prepared from 1-(2-chlorobenzyl)-3-ethyl-2-propionylindole-6-carboxylic acid (46 mg) in a similar manner to that of Example 3.

25 NMR (CDCl₃, δ) : 1.16 (3H, t, J=7Hz), 1.38 (3H, t, J=7Hz), 2.96 (2H, q, J=7Hz), 3.14 (2H, q, J=7Hz), 5.72 (2H, s), 6.25 (1H, d, J=8Hz), 7.00 (1H, t, J=8Hz), 7.14 (1H, t, J=8Hz), 7.39 (1H, d, J=8Hz), 7.56 (1H, d, J=8Hz), 7.79 (1H, s), 7.80 (1H, d, J=8Hz)

30

Example 22

The following compounds described in 1) to 6) were prepared by reacting the compound (I-2) obtained in Example 2

35

BAD ORIGINAL



- 98 -

or Example 34-19), and a suitable amine (IV) in a similar manner to that of Example 3.

- (1) 3-Acetyl-1-(2-chlorobenzyl)-N,N-dimethyl-2-propylindole-
5 6-carboxamide
mp : 150-153°C
NMR (CDCl₃, δ) : 1.03 (3H, t, J=7Hz), 1.63 (2H, m),
2.72 (3H, s), 2.98 (6H, br s), 3.09 (2H, m), 5.44
(2H, s), 6.26 (1H, dd, J=1, 8Hz), 7.03 (1H, dt,
10 J=1, 8Hz), 7.20 (1H, dt, J=1, 8Hz), 7.29 (1H, s),
7.35 (1H, d, J=8Hz), 7.43 (1H, dd, J=1, 8Hz), 8.03
(1H, d, J=8Hz)
- (2) 3-Acetyl-1-(2-chlorobenzyl)-N-cyclopropylmethyl-2-
15 propylindole-6-carboxamide
mp : 158-162°C
NMR (CDCl₃, δ) : 0.28 (2H, m), 0.55 (2H, m), 1.03 (3H,
t, J=7Hz), 1.05 (1H, m), 1.60 (2H, m), 2.72 (3H,
s), 3.04 (2H, m), 3.31 (2H, m), 5.49 (2H, s), 6.22
20 (1H, d, J=8Hz), 6.28 (1H, m), 7.03 (1H, t, J=8Hz),
7.22 (1H, t, J=8Hz), 7.45 (1H, d, J=8Hz), 7.61 (1H,
dd, J=1, 8Hz), 7.82 (1H, d, J=1Hz), 8.05 (1H, d,
J=8Hz)
- (3) 3-Acetyl-1-(2-chlorobenzyl)-N-(2-pyridylmethyl)-2-
25 propylindole-6-carboxamide
mp : 172-175°C
NMR (CDCl₃, δ) : 1.02 (3H, t, J=7Hz), 1.63 (2H, m),
2.73 (3H, s), 3.07 (2H, m), 4.75 (2H, d, J=5Hz),
30 5.51 (2H, s), 6.22 (1H, d, J=8Hz), 7.02 (1H, t,
J=8Hz), 7.15-7.27 (2H, m), 7.33 (1H, d, J=8Hz),
7.44 (1H, d, J=8Hz), 7.58-7.76 (3H, s), 7.88 (1H,
s), 8.07 (1H, d, J=8Hz), 8.56 (1H, m).
- (4) 3-Acetyl-1-(2-chlorobenzyl)-6-(morpholinocarbonyl)-2-
- 35

- 99 -

propylindole

NMR (CDCl₃ δ) : 1.03 (3H, t, J=7Hz), 1.63 (2H, m),
2.73 (3H, s), 3.09 (2H, m), 3.63 (8H, br s), 5.44
(2H, s), 6.23 (1H, d, J=8Hz), 7.06 (1H, t, J=8Hz),
5 7.2-7.4 (3H, m), 7.46 (1H, d, J=8Hz), 8.06 (1H, d,
J=8Hz)

(5) 3-Acetyl-1-(2-chlorobenzyl)-N-phenylsulfonyl-2-
propylindole-6-carboxamide

10 mp : 206-208°C

NMR (CDCl₃, δ) : 0.99 (3H, t, J=7Hz), 1.54 (2H, m),
2.72 (3H, s), 3.02 (2H, m), 5.43 (2H, s), 6.13 (1H,
d, J=8Hz), 7.00 (1H, t, J=8Hz), 7.21 (1H, t,
J=8Hz), 7.43 (1H, d, J=8Hz), 7.5-7.7 (4H, m), 7.77
15 (1H, s), 8.08 (1H, d, J=8Hz), 8.13-8.18 (2H, m),
8.81 (1H, br s)

(6) 1-(2-Chlorobenzyl)-3-formyl-N-phenylsulfonyl-2-
propylindole-6-carboxamide

20 mp : 242-245°C

NMR (CDCl₃, δ) : 0.87 (3H, t, J=7Hz), 1.49 (2H, m),
3.07 (2H, t, J=7Hz), 5.66 (2H, s), 6.32 (1H, d,
J=8Hz), 7.18 (1H, t, J=8Hz), 7.33 (1H, t, J=8Hz),
7.55-7.75 (4H, m), 7.88 (1H, m), 7.96 (1H, s), 7.98
25 (1H, d, J=8Hz), 8.09 (1H, s), 8.23 (1H, d, J=8Hz)

(7) 1-(2-Chlorobenzyl)-3-formyl-2-propyl-N-(1H-tetrazol-5-
yl)indole-6-carboxamide

mp : 275°C (dec.)

30 NMR (DMSO-d₆, δ) : 0.90 (3H, t, J=7Hz), 1.54 (2H, m),
3.13 (2H, t, J=7Hz), 5.69 (2H, s), 6.38 (1H, d,
J=8Hz), 7.19 (1H, t, J=8Hz), 7.33 (1H, t, J=8Hz),
7.60 (1H, d, J=8Hz), 8.03 (1H, d, J=8Hz), 8.31 (1H,
s), 8.32 (1H, d, J=8Hz), >10 (1H, s)

35

- 100 -

Example 23

1-Hydroxybenzotriazole (68 mg) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (72 mg) were added to a solution of 1-(2-chlorobenzyl)-3-isobutyryl-2-propylindole-6-carboxylic acid (100 mg) in dimethylformamide (3 ml), and the mixture was stirred at 20°C overnight, then hydroxylamine hydrochloride (35 mg) and diisopropylethylamine (0.088 ml) were added. After stirred at 20°C for 2 hours, the reaction mixture was partitioned between ethyl acetate and water. The organic phase was washed with 1N hydrochloric acid and brine, dried over sodium sulfate, and evaporated in vacuo. The residue was purified by preparative thin layer chromatography with 10% methanol in chloroform and recrystallization from ethyl acetate to give 1-(2-chlorobenzyl)-3-isobutyryl-2-propylindole-6-carbohydroxamic acid (67 mg) as pale red crystals.

mp : 185-186°C

NMR (CDCl₃, δ) : 1.00 (3H, t, J=8Hz), 1.28 (6H, d, J=8Hz), 1.60 (2H, sextet, J=8Hz), 3.02-3.06 (2H, m), 3.53 (2H, septet, J=8Hz), 5.47 (2H, s), 6.20 (1H, dd, J=1, 8Hz), 7.03 (1H, t, J=8Hz), 7.20 (1H, t, J=8Hz), 7.46 (1H, d, J=8Hz), 7.57 (1H, d, J=8Hz), 7.77 (1H, s), 7.97 (1H, d, J=8Hz)

Example 24

The following compounds described in 1) to 2) were prepared by reacting the compound (I-2) obtained in Example 5 and a suitable amine (IV) in a similar manner to that of Example 23.

(1) 1-(2-Chlorobenzyl)-3-isobutyryl-O-methyl-2-propylindole-6-carbohydroxamic acid

NMR (CDCl₃, δ) : 1.00 (3H, t, J=8Hz), 1.30 (6H, d, J=8Hz), 1.54-1.66 (2H, m), 3.00-3.06 (2H, m), 3.53 (1H, septet, J=8Hz), 3.86 (3H, s), 5.49 (2H, s),

- 101 -

6.22 (1H, dd, J=1, 8Hz), 7.03 (1H, dt, J=1, 8Hz),
7.23 (1H, dt, J=1, 8Hz), 7.46 (1H, dd, J=1, 8Hz),
7.56 (1H, dd, J=1, 8Hz), 7.75 (1H, d, J=1Hz), 7.96
(1H, d, J=8Hz), 8.82 (1H, s)

5

(2) 1-(2-Chlorobenzyl)-3-isobutyl-2-propyl-N-(2-pyridylmethyl)indole-6-carboxamide

NMR (CDCl₃, δ) : 1.00 (3H, t, J=8Hz), 1.30 (6H, d,
J=8Hz), 1.62 (2H, sextet, J=8Hz), 3.03-3.07 (2H,
10 m), 3.57 (1H, septet, J=8Hz), 4.66 (2H, d, J=6Hz),
5.50 (2H, s), 6.24 (1H, dd, J=1, 8Hz), 7.02 (1H,
dt, J=1, 8Hz), 7.18-7.24 (2H, m), 7.33 (1H, d,
J=8Hz), 7.45 (1H, d, J=8Hz), 7.62-7.68 (2H, m),
7.72 (1H, dd, J=1, 8Hz), 7.88 (1H, d, J=1Hz), 7.98
15 (1H, d, J=8Hz), 8.56 (1H, d, J=6Hz)

Example 25

The following compounds described in 1) to 2) were
prepared by reacting the compound (II) obtained in
20 Preparation 8 (2) and a suitable halide (III) in a similar
manner to that of Example 1.

(1) 1-(4-Chloro-2-fluorobenzyl)-3-isobutyryl-2-propylindole-
6-carboxamide

25

mp : 200-202°C

IR (KBr) : 3380, 3195, 1650, 1620 cm⁻¹

NMR (CDCl₃, δ) : 1.03 (3H, t, J=7Hz), 1.30 (6H, d,
J=7Hz), 1.52-1.65 (2H, m), 3.06-3.10 (2H, m), 3.49-
3.59 (1H, m), 5.47 (2H, s), 6.34 (1H, ddd, J=8, 8,
30 1Hz), 6.94 (1H, dd, J=8, 1Hz), 7.19 (1H, d, J=8Hz),
7.60 (1H, d, J=8Hz), 7.89 (1H, s), 7.97 (1H, d,
J=8Hz)

MASS (m/z) : 415 (M⁺+1), 76 (bp)

35 (2) 3-Isobutyryl-(2-methoxycarbonylbenzyl)-2-propylindole-6-

- 102 -

carboxamide

mp : 170-172°C

IR (KBr) : 3420, 1720, 1650 cm^{-1}

5 NMR (CDCl_3 , δ) : 1.00 (3H, t, $J=7\text{Hz}$), 1.33 (6H, d, $J=7\text{Hz}$), 1.56-1.69 (2H, m), 3.00-3.06 (2H, m), 3.54-3.63 (1H, m), 4.02 (3H, s), 5.91 (2H, s), 6.69 (1H, d, $J=7.5\text{Hz}$), 7.24-7.36 (1H, m), 7.63 (1H, dd, $J=8$, 1Hz), 7.80 (1H, s), 7.99 (1H, d, $J=8\text{Hz}$), 8.12-8.16 (1H, m)

10 MASS (m/z) : 421 ($\text{M}^+ + 1$)

Example 26

A mixture of 3-isobutyryl-2-propylindole-6-carboxamide (100 mg), 4-chlorobenzyl bromide (113 mg) and potassium carbonate (152 mg) in dimethylformamide (2 ml) was heated at 60°C for 2 hours, and partitioned between ethyl acetate and water. The organic layer was washed with water and brine, and dried over magnesium sulfate. After evaporation of solvent, the residue was crystallized from a mixture of ethyl acetate and hexane. The crude crystals were recrystallized from a mixture of ethyl acetate and hexane to give 1-(4-chlorobenzyl)-3-isobutyryl-2-propylindole-6-carboxamide (97 mg) as colorless crystals.

mp : 183-184°C

25 NMR (CDCl_3 , δ) : 1.01 (3H, t, $J=7\text{Hz}$), 1.29 (6H, d, $J=7\text{Hz}$), 1.50-1.64 (2H, m), 3.06-3.12 (2H, m), 3.55 (2H, septet, $J=7\text{Hz}$), 5.42 (2H, s), 6.87 (2H, d, $J=8\text{Hz}$), 7.25 (2H, d, $J=8\text{Hz}$), 7.60 (1H, dd, $J=1$, 8Hz), 7.87 (1H, d, $J=1\text{Hz}$), 7.95 (1H, d, $J=8\text{Hz}$)

30

Example 27

The following compounds described in 1) to 8) were prepared by reacting the compound (II) obtained in Preparation 8 (2) or Preparation 15 (3), and a suitable halide (III) in a similar manner to that of Example 26.

35



- 103 -

(1) 1-Benzyl-3-isobutyryl-2-propylindole-6-carboxamide

mp : 164-166°C

NMR (CDCl₃, δ) : 1.00 (3H, t, J=7Hz), 1.29 (6H, d, J=7Hz), 1.60 (2H, sextet, J=7Hz), 3.09-3.13 (2H, m), 3.55 (2H, septet, J=7Hz), 5.46 (2H, s), 6.96-6.98 (2H, m), 7.24-7.32 (2H, m), 7.61 (1H, d, J=8Hz), 7.91 (1H, s), 7.95 (1H, d, J=8Hz)

(2) 1-(3-Chlorobenzyl)-3-isobutyryl-2-propylindole-6-carboxamide

mp : 164-166°C

NMR (CDCl₃, δ) : 1.00 (3H, t, J=7Hz), 1.30 (6H, d, J=7Hz), 1.50-1.65 (2H, m), 3.06-3.12 (2H, m), 3.55 (2H, septet, J=7Hz), 5.42 (2H, s), 6.78 (1H, dd, J=1, 8Hz), 6.96 (1H, d, J=1Hz), 7.18-7.27 (2H, m), 7.60 (1H, d, J=8Hz), 7.88 (1H, s), 7.95 (1H, d, J=8Hz)

(3) 3-Isobutyryl-2-propyl-1-(2-trifluoromethylbenzyl)indole-6-carboxamide

mp : 86-87°C

NMR (CDCl₃, δ) : 0.99 (3H, t, J=7Hz), 1.30 (6H, d, J=7Hz), 1.52-1.65 (2H, m), 2.98-3.04 (2H, m), 3.56 (2H, septet, J=7Hz), 5.62 (2H, s), 6.33 (1H, d, J=8Hz), 7.30 (1H, t, J=1Hz), 7.38 (1H, t, J=1Hz), 7.64 (1H, d, J=8Hz), 7.75 (1H, d, J=8Hz), 7.84 (1H, s), 7.98 (1H, d, J=8Hz)

(4) 3-Isobutyryl-1-(2-phenylbenzyl)-2-propylindole-6-carboxamide

mp : 162-164°C

NMR (CDCl₃, δ) : 0.89 (3H, t, J=7Hz), 1.27 (6H, d, J=7Hz), 1.36-1.50 (2H, m), 2.90-2.96 (2H, m), 3.53 (2H, septet, J=7Hz), 5.32 (2H, s), 6.48 (1H, d, J=8Hz), 7.10-7.16 (1H, m), 7.30-7.34 (2H, m), 7.42-

- 104 -

7.84 (3H, m), 7.52-7.55 (2H, m), 7.60 (1H, d, J=8Hz), 7.84 (1H, s), 7.93 (1H, d, J=8Hz)

(5) 1-[(5-Chlorothiophen-2-yl)methyl]-3-isobutyryl-2-propylindole-6-carboxamide

mp : 178-180°C

NMR (CDCl₃, δ) : 1.07 (3H, t, J=7Hz), 1.27 (6H, d, J=7Hz), 1.65 (2H, sextet, J=7Hz), 3.15-3.20 (2H, m), 3.54 (2H, septet, J=7Hz), 5.46 (2H, s), 6.59 (1H, d, J=2Hz), 6.72 (2H, d, J=2Hz), 7.60 (1H, d, J=8Hz), 7.92 (1H, d, J=8Hz), 8.04 (1H, s)

(6) 3-Isobutyryl-1-phenethyl-2-propylindole-6-carboxamide

mp : 180-181°C

NMR (CDCl₃, δ) : 1.02 (3H, t, J=7Hz), 1.26 (6H, d, J=7Hz), 1.61 (2H, septet, J=7Hz), 2.88-2.92 (2H, m), 3.10 (2H, t, J=7Hz), 3.52 (2H, septet, J=7Hz), 4.42 (2H, t, J=7Hz), 7.05-7.09 (2H, m), 7.22-7.32 (3H, m), 7.52 (1H, d, J=8Hz), 7.92 (1H, d, J=8Hz), 7.96 (1H, s)

(7) 1-(2-Chlorobenzyl)-3-methoxyacetyl-2-propylindole-6-carboxamide

mp : 165-167°C

NMR (DMSO-d₆, δ) : 0.92 (3H, t, J=8Hz), 1.46 (2H, sextet, J=8Hz), 3.01-3.05 (2H, m), 3.42 (3H, s), 4.68 (2H, s), 5.62 (2H, s), 6.22 (1H, d, J=8Hz), 7.16 (1H, t, J=8Hz), 7.28 (1H, br s), 7.32 (1H, t, J=8Hz), 7.56 (1H, d, J=8Hz), 7.92 (1H, d, J=8Hz), 7.93 (1H, br s), 8.01 (1H, s)

(8) 1-(6-Chloro-3,4-methylenedioxybenzyl)-3-methoxyacetyl-2-propylindole-6-carboxamide

mp : 204-206°C

NMR (DMSO-d₆, δ) : 0.95 (3H, t, J=8Hz), 1.50 (2H,

- 105 -

sextet, $J=8\text{Hz}$), 3.02-3.06 (2H, m), 3.40 (3H, s),
4.70 (2H, s), 5.51 (1H, s), 5.98 (2H, s), 7.23 (1H,
s), 7.32 (1H, br s), 7.80 (1H, d, $J=8\text{Hz}$), 7.93 (1H,
d, $J=8\text{Hz}$), 7.96 (1H, br s), 8.02 (1H, s)

5

Example 28

The following compounds described in 1) to 16) were
prepared by reacting the compound (II) obtained in
Preparation 2, Preparation 6 (1), Preparation 9, Preparation
10, Preparation 12, Preparation 13 (4) or Preparation 14 (5)
and a suitable halide (III) in a similar manner to that of
Example 1.

(1) Methyl 1-(2-fluorobenzyl)-3-isobutyryl-2-propylindole-6-
carboxylate

15

mp : 120-121.5°C

IR (KBr) : 1710, 1700, 1660 cm^{-1}

NMR (CDCl_3 , δ) : 1.02 (3H, t, $J=7\text{Hz}$), 1.29 (6H, d,
 $J=7\text{Hz}$), 1.55-1.64 (2H, m), 3.06-3.12 (2H, m), 3.51-
3.61 (1H, m), 3.92 (3H, s), 5.50 (2H, s), 6.43 (1H,
t, $J=7.5\text{Hz}$), 6.95 (1H, t, $J=7\text{Hz}$), 7.10-7.17 (1H,
m), 7.22-7.28 (1H, m), 7.95 (2H, s), 8.02 (1H, s)

20

MASS (m/z) : 396 (M^++1), 76 (bp)

(2) Methyl 1-(2-bromobenzyl)-3-isobutyryl-2-propylindole-6-
carboxylate

25

mp : 90-92°C

IR (KBr) : 1705, 1650 cm^{-1}

NMR (CDCl_3 , δ) : 1.02 (3H, t, $J=7\text{Hz}$), 1.30 (6H, d,
 $J=7\text{Hz}$), 1.56-1.67 (2H, m), 3.04 (2H, t, $J=7\text{Hz}$),
3.52-3.61 (1H, m), 3.93 (3H, s), 5.47 (2H, s), 6.20
(1H, t, $J=7.5\text{Hz}$), 7.06-7.18 (2H, m), 7.65 (1H, t,
 $J=7.5\text{Hz}$), 7.95 (1H, s), 7.97 (2H, s)

30

MASS (m/z) : 458 (M^++1+2), 458 (M^++1), 76 (bp)

35

BAD ORIGINAL

- 106 -

(3) Methyl 1-(2-iodobenzyl)-3-isobutyryl-2-propylindole-6-carboxylate

IR (KBr) : 1710, 1650, 1430 cm^{-1}

5 NMR (CDCl_3 , δ) : 1.03 (3H, t, $J=7\text{Hz}$), 1.30 (6H, d, $J=7\text{Hz}$), 1.53-1.67 (2H, m), 2.98-3.05 (2H, m), 3.53-3.62 (1H, m), 3.93 (3H, s), 5.37 (2H, s), 6.16 (1H, t, $J=7.5\text{Hz}$), 6.99 (1H, t, $J=7.5\text{Hz}$), 7.12 (1H, t, $J=7.5\text{Hz}$), 7.90-7.97 (4H, m)

MASS (m/z) : 504 (M^++1)

10

(4) Methyl 3-isobutyryl-1-(2-methylbenzyl)-2-propylindole-6-carboxylate

mp : 99-102°C

IR (KBr) : 1705, 1650, 1285 cm^{-1}

15 NMR (CDCl_3 , δ) : 1.00 (3H, t, $J=7\text{Hz}$), 1.30 (6H, d, $J=7\text{Hz}$), 1.54-1.69 (2H, m), 2.50 (3H, s), 3.00-3.06 (2H, m), 3.51-3.65 (1H, m), 3.89 (3H, s), 5.39 (2H, s), 6.17 (1H, t, $J=7.5\text{Hz}$), 6.98 (1H, t, $J=7.5\text{Hz}$), 7.18 (1H, t, $J=7.5\text{Hz}$), 7.25 (1H, d, $J=7.5\text{Hz}$), 7.92 (1H, s), 7.96 (2H, s)

20

MASS (m/z) : 392 (M^++1)

(5) Methyl 3-isobutyryl-1-(2-methoxybenzyl)-2-propylindole-6-carboxylate

25 mp : 103-105°C

IR (KBr) : 1710, 1650 cm^{-1}

30 NMR (CDCl_3 , δ) : 1.01 (3H, t, $J=7\text{Hz}$), 1.30 (6H, d, $J=7\text{Hz}$), 1.56-1.68 (2H, m), 3.05-3.10 (2H, m), 3.53-3.62 (1H, m), 3.90 (3H, s), 3.98 (3H, s), 5.44 (2H, s), 6.27 (1H, d, $J=7.5\text{Hz}$), 6.74 (1H, t, $J=7.5\text{Hz}$), 6.94 (1H, d, $J=7.5\text{Hz}$), 7.25 (1H, t, $J=7.5\text{Hz}$), 7.95 (2H, s), 8.00 (1H, d, $J=7.5\text{Hz}$)

MASS (m/z) : 408 (M^++1), 76 (bp)

35 (6) Methyl 1-(2-cyanobenzyl)-3-isobutyryl-2-propylindole-6-

BAD ORIGINAL

- 107 -

carboxylate

mp : 159-161°C

IR (KBr) : 2220, 1730, 1660 cm^{-1}

5 NMR (CDCl_3 , δ) : 1.04 (3H, t, $J=7\text{Hz}$), 1.30 (6H, d, $J=7\text{Hz}$), 1.52-1.65 (2H, m), 3.03-3.08 (2H, m), 3.53-3.60 (1H, m), 3.92 (3H, s), 5.66 (2H, s), 6.44-6.49 (1H, m), 7.38-7.43 (2H, m), 7.76-7.80 (1H, m), 7.95 (1H, s), 7.98 (2H, s)

10 MASS (m/z) : 403 (M^++1), 76 (bp)

(7) Methyl 3-isobutyryl-1-(2-nitrobenzyl)-2-propylindole-6-carboxylate

mp : 165.5-166.5°C

IR (KBr) : 1705, 1650, 1530, 1520 cm^{-1}

15 NMR (CDCl_3 , δ) : 1.00 (3H, t, $J=7\text{Hz}$), 1.31 (6H, d, $J=7\text{Hz}$), 1.56-1.65 (2H, m), 3.03 (2H, t, $J=7\text{Hz}$), 3.54-3.65 (1H, m), 3.90 (3H, s), 5.89 (2H, s), 6.27 (1H, d, $J=7.5\text{Hz}$), 7.40-7.51 (2H, m), 7.89 (1H, s), 8.00 (2H, s), 8.30 (1H, d, $J=7.5\text{Hz}$)

20 MASS (m/z) : 423 (M^++1), 76 (bp)

(8) Methyl 1-(2,6-dichlorobenzyl)-3-isobutyryl-2-propylindole-6-carboxylate

mp : 129.5-132°C

25 IR (KBr) : 1710, 1660, 1430- cm^{-1}

NMR (CDCl_3 , δ) : 0.96 (3H, t, $J=7\text{Hz}$), 1.27 (6H, d, $J=7\text{Hz}$), 1.38-1.50 (2H, m), 3.15-3.20 (2H, m), 3.47-3.60 (1H, m), 3.92 (3H, s), 5.70 (2H, s), 7.17-7.39 (3H, m), 7.88 (2H, s), 8.03 (1H, s)

30 MASS (m/z) : 446 (M^++1)

(9) Methyl 1-(2-chloro-4-fluorobenzyl)-3-isobutyryl-2-propylindole-6-carboxylate

mp : 140-141°C

35 IR (KBr) : 1705, 1649, 1488, 1279 cm^{-1}

BAD ORIGINAL

- 108 -

NMR (CDCl₃, δ) : 1.03 (3H, t, J=7Hz), 1.40 (6H, d, J=7Hz), 1.52-1.66 (2H, m), 3.01-3.06 (2H, m), 3.52-3.60 (1H, m), 3.93 (3H, s), 5.48 (2H, s), 6.20-6.25 (1H, m), 6.79 (1H, ddd, J=7.5, 7.5, 1Hz), 7.21-7.25 (1H, m), 7.94 (1H, s), 7.97 (2H, s)
5
MASS (m/z) : 430 (M⁺+1), 76 (bp)

(10) Methyl 1-(4-bromo-2-fluorobenzyl)-3-isobutyryl-2-propylindole-6-carboxylate
10
mp : 110-111.5°C.
IR (KBr) : 1705, 1649, 1488, 1279 cm⁻¹
NMR (CDCl₃, δ) : 1.03 (3H, t, J=7Hz), 1.29 (6H, d, J=7Hz), 1.53-1.65 (2H, m), 3.05-3.10 (2H, m), 3.51-3.60 (1H, m), 3.94 (3H, s), 5.44 (2H, s), 6.28 (1H, t, J=7.5Hz), 7.10 (1H, dd, J=7.5, 1Hz), 7.35 (1H, d, J=7.5Hz), 7.96 (1H, s)
15
MASS (m/z) : 476 (M⁺+1), 474 (M⁺), 76 (bp)

(11) Methyl 3-benzoyl-1-(2-chlorobenzyl)-2-propylindole-6-carboxylate
20
NMR (CDCl₃, δ) : 0.94 (3H, t, J=8Hz), 1.56-1.70 (2H, m), 2.93-2.98 (2H, m), 3.87 (3H, s), 5.55 (2H, s), 6.33 (1H, ddd, J=1, 8Hz), 7.08 (1H, dt, J=1, 8Hz), 7.21 (1H, d, J=8Hz), 7.22-7.28 (1H, m), 7.46-7.52 (3H, m), 7.57-7.63 (1H, m), 7.72-7.82 (3H, m), 7.93 (1H, d, J=1Hz)
25

(12) Methyl 1-(2-chlorobenzyl)-3-cyano-2-propylindole-6-carboxylate
30
mp : 132-133°C
IR (KBr) : 2215, 1709, 1284 cm⁻¹
NMR (CDCl₃, δ) : 1.01 (3H, t, J=7Hz), 1.70 (2H, sextet, J=7Hz), 2.89 (2H, t, J=7.5Hz), 3.92 (3H, s), 5.49 (2H, s), 6.24 (1H, d, J=7.5Hz), 7.08 (1H, t, J=7.5Hz), 7.22-7.28 (1H, m), 7.47 (1H, d,
35

BAD ORIGINAL

- 109 -

J=7.5Hz), 7.77 (1H, d, J=7.5Hz), 7.95-8.00 (2H, m)
MASS (m/z) : 367 ($M^+ + 1$), 76 (bp)

5 (13) Methyl 1-(2-chlorobenzyl)-2-ethyl-3-isobutyrylindole-6-carboxylate

NMR (CDCl₃, δ) : 1.22 (3H, t, J=7Hz), 1.31 (6H, d, J=7Hz), 3.08 (2H, q, J=7Hz), 3.56 (1H, m), 3.91 (3H, s), 5.50 (2H, s), 6.23 (1H, d, J=8Hz), 7.04 (1H, t, J=8Hz), 7.22 (1H, t, J=8Hz), 7.46 (1H, d, J=8Hz), 7.93-7.98 (3H, m)

(14) Methyl 1-(2-chlorobenzyl)-3-isobutyryl-2-methylindole-6-carboxylate

15 NMR (CDCl₃, δ) : 1.32 (6H, d, J=7Hz), 2.71 (3H, s), 3.56 (1H, m), 3.92 (3H, s), 5.52 (2H, s), 6.24 (1H, d, J=8Hz), 7.05 (1H, t, J=8Hz), 7.23 (1H, t, J=8Hz), 7.46 (1H, d, J=8Hz), 7.92-8.05 (3H, m)

20 (15) Methyl 1-(2-chlorobenzyl)-3-isobutyryl-2-methoxymethylindole-6-carboxylate

NMR (CDCl₃, δ) : 1.29 (6H, d, J=7Hz), 3.31 (3H, s), 3.55 (1H, m), 3.89 (3H, s), 4.91 (2H, s), 5.63 (2H, s), 6.23 (1H, d, J=8Hz), 7.02 (1H, t, J=8Hz), 7.19 (1H, t, J=8Hz), 7.44 (1H, d, J=8Hz), 7.95-8.02 (3H, m)

(16) Methyl 1-(2-chlorobenzyl)-3-isobutyrylindole-6-carboxylate

30 NMR (CDCl₃, δ) : 1.26 (6H, d, J=7Hz), 3.28 (1H, m), 3.93 (3H, s), 5.52 (2H, s), 6.77 (1H, d, J=8Hz), 7.18 (1H, t, J=8Hz), 7.29 (1H, t, J=8Hz), 7.48 (1H, d, J=8Hz), 7.89 (1H, s), 8.02 (1H, d, J=8Hz), 8.10 (1H, s), 8.49 (1H, d, J=8Hz)

35 Example 29

BAD ORIGINAL

- 110 -

The following compounds described in 1) to 2) were prepared from the compound (II) obtained in Preparation 1 (5) and Preparation 2 in a similar manner to that of Example 26.

- 5 (1) Methyl 3-isobutyryl-2-propyl-1-(2-pyridylmethyl)indole-6-carboxylate

NMR (CDCl₃, δ) : 1.01 (3H, t, J=7Hz), 1.30 (6H, d, J=7Hz), 1.60 (2H, sextet, J=7Hz), 3.12-3.16 (2H, m), 3.56 (2H, septet, J=7Hz), 3.90 (3H, s), 5.58 (2H, s), 6.58 (1H, d, J=8Hz), 7.22 (1H, dd, J=5, 8Hz), 7.55 (1H, dt, J=1, 8Hz), 7.94 (2H, s), 8.02 (1H, s), 8.63 (1H, dd, J=1, 5Hz)

10

- 15 (2) Methyl 3-acetyl-1-(6-chloro-3,4-methylenedioxybenzyl)-2-propylindole-6-carboxylate

mp : 210-212°C

NMR (CDCl₃, δ) : 1.04 (3H, t, J=7Hz), 1.63 (2H, sextet, J=7Hz), 2.37 (3H, s), 3.04-3.08 (2H, m), 3.92 (3H, s), 5.40 (2H, s), 5.70 (1H, s), 5.90 (2H, s), 6.92 (1H, s), 7.95 (1H, s), 7.97 (1H, d, J=8Hz), 8.04 (1H, d, J=8Hz)

20

Example 30

To a solution of methyl 3-acetyl-1-(2-chlorobenzyl)-2-ethylindole-6-carboxylate (110 mg) in tetrahydrofuran (5 ml) was added 1M solution of boran in tetrahydrofuran (0.6 ml) in one portion at 0°C. The mixture was stirred at 20°C for 1 hour, then quenched with water and extracted with ethyl acetate. The organic phase was washed with brine, dried over magnesium sulfate and evaporated in vacuo. The residue was chromatographed on silica gel eluting with a mixture of hexane and ethyl acetate (2:1) to give methyl 1-(2-chlorobenzyl)-2,3-diethylindole-6-carboxylate (42 mg) as colorless crystals.

25

30

35 mp : 86-88°C

BAD ORIGINAL



- 111 -

IR (KBr) : 1710, 1240 cm^{-1}

NMR (CDCl_3 , δ) : 1.13 (3H, t, $J=7\text{Hz}$), 1.30 (3H, t, $J=7\text{Hz}$), 2.69 (2H, t, $J=7\text{Hz}$), 2.79 (2H, q, $J=7\text{Hz}$), 3.90 (3H, s), 5.44 (2H, s), 6.17 (1H, d, $J=8\text{Hz}$), 7.00 (1H, t, $J=8\text{Hz}$), 7.19 (1H, t, $J=8\text{Hz}$), 7.42 (1H, d, $J=7.5\text{Hz}$), 7.60 (1H, d, $J=8\text{Hz}$), 7.80 (1H, d, $J=8\text{Hz}$), 7.88 (1H, s)

MASS (m/z) : 356 (M^++1)10 Example 31

Methyl 1-(2-chlorobenzyl)-2-propylindole-6-carboxylate (400 mg) was prepared from methyl 2-propylindole-6-carboxylate (350 mg) and 2-chlorobenzyl bromide (364 mg) in a similar manner to that of Example 1.

15 NMR (CDCl_3 , δ) : 0.99 (3H, t, $J=8\text{Hz}$), 1.74 (2H, sextet, $J=8\text{Hz}$), 2.60 (2H, t, $J=8\text{Hz}$), 3.87 (3H, s), 5.43 (2H, s), 6.16 (1H, d, $J=8\text{Hz}$), 6.43 (1H, s), 7.00 (1H, t, $J=8\text{Hz}$), 7.18 (1H, t, $J=8\text{Hz}$), 7.43 (1H, d, $J=8\text{Hz}$), 7.60 (1H, d, $J=8\text{Hz}$), 7.80 (1H, d, $J=8\text{Hz}$), 7.90 (1H, s)

Example 32

To a stirred solution of dimethylformamide (3 ml) and phosphorus oxychloride (0.056 ml) was added methyl 2-propylindole-6-carboxylate (187 mg), and the mixture was stirred at 0°C for 20 minutes. The resulting mixture was poured into ammonia water (3 ml) and extracted with ethyl acetate. The combined organic phase was washed with brine, then dried over sodium sulfate and evaporated in vacuo. The residue was chromatographed on silica gel to give methyl 1-(2-chlorobenzyl)-3-formyl-2-propylindole-6-carboxylate (153 mg) as colorless oil.

35 NMR (CDCl_3 , δ) : 1.00 (3H, t, $J=7\text{Hz}$), 1.66 (2H, m), 3.01 (2H, t, $J=7\text{Hz}$), 3.90 (3H, s), 5.48 (2H, s), 6.29 (1H, d, $J=8\text{Hz}$), 7.06 (1H, t, $J=8\text{Hz}$), 7.24 (1H,



- 112 -

t, J=8Hz), 7.47 (1H, d, J=8Hz), 7.91 (1H, s), 8.01 (1H, d, J=8Hz), 8.37 (1H, d, J=8Hz), >10 (1H, s)

Example 33

5 Methyl 1-(2-chlorobenzyl)-3-phenylacetyl-2-propylindole-6-carboxylate (230 mg) was prepared from methyl 1-(2-chlorobenzyl)-2-propylindole-6-carboxylate (380 mg) and phenylacetyl chloride (189 mg) in a similar manner to that of Preparation 1 (5).

10 NMR (CDCl₃, δ) : 0.97 (3H, t, J=8Hz), 1.55-1.67 (2H, m), 3.02-3.07 (2H, m), 3.91 (3H, s), 4.42 (2H, s), 5.52 (2H, s), 6.24 (1H, d, J=8Hz), 7.05 (1H, t, J=8Hz), 7.20-7.40 (6H, m), 7.46 (1H, d, J=8Hz), 7.97 (1H, s), 7.99 (1H, d, J=8Hz), 8.11 (1H, d, J=8Hz)

15

Example 34

The following compounds described in 1) to 21) were prepared from the compound (I-1) obtained in Example 28, Example 29, Example 30, Example 32 or Example 33 in a similar manner to that of Example 2.

20

(1) 1-(2-Fluorobenzyl)-3-isobutyryl-2-propylindole-6-carboxylic acid

25 mp : 212-213°C

IR (KBr) : 1685, 1650 cm⁻¹

NMR (CDCl₃, δ) : 1.03 (3H, t, J=7Hz), 1.30 (6H, d, J=7Hz), 1.55-1.68 (2H, m), 3.09-3.14 (2H, m), 3.52-3.62 (1H, m), 5.50 (2H, s), 6.47 (1H, t, J=7.5Hz), 6.97 (1H, t, J=7.5Hz), 7.15 (1H, t, J=7.5Hz), 7.24-7.30 (1H, m), 7.95-8.04 (2H, m), 8.08 (1H, s)

30

MASS (m/z) : 380 (M⁺-1)

(2) 1-(2-Bromobenzyl)-3-isobutyryl-2-propylindole-6-carboxylic acid

35

- 113 -

mp : 193-194°C

IR (KBr) : 1690, 1670 cm^{-1}

NMR (CDCl_3 , δ) : 1.03 (3H, t, $J=7\text{Hz}$), 1.31 (6H, d, $J=7\text{Hz}$), 1.57-1.65 (2H, m), 3.01-3.07 (2H, m), 3.52-3.61 (1H, m), 5.49 (2H, s), 6.22 (1H, t, $J=7.5\text{Hz}$), 7.07-7.18 (2H, m), 7.66 (1H, t, $J=7.5\text{Hz}$), 7.97-8.01 (3H, m)

MASS (m/z) : 442 (M^+), 440 (M^+-2)

10 (3) 1-(2-Iodobenzyl)-3-isobutyryl-2-propylindole-6-carboxylic acid

mp : 210°C

IR (KBr) : 1710, 1640, 1435, 1200 cm^{-1}

15 NMR (CDCl_3 , δ) : 1.04 (3H, t, $J=7\text{Hz}$), 1.31 (6H, d, $J=7\text{Hz}$), 1.55-1.68 (2H, m), 3.00-3.06 (2H, m), 3.53-3.62 (1H, m), 5.38 (2H, s), 6.18 (1H, d, $J=7.5\text{Hz}$), 6.99 (1H, t, $J=7.5\text{Hz}$), 7.14 (1H, t, $J=7.5\text{Hz}$), 7.94 (1H, d, $J=7.5\text{Hz}$), 7.97-8.03 (3H, m)

MASS (m/z) : 488 (M^+-1), 61 (bp)

20

(4) 3-Isobutyryl-1-(2-methylbenzyl)-2-propylindole-6-carboxylic acid

mp : 186-188°C

IR (KBr) : 1690 cm^{-1}

25 NMR (CDCl_3 , δ) : 1.01 (3H, t, $J=7\text{Hz}$), 1.31 (6H, d, $J=7\text{Hz}$), 1.56-1.69 (2H, m), 2.50 (3H, s), 3.02-3.09 (2H, m), 3.52-3.67 (1H, m), 5.39 (2H, s), 6.17 (1H, d, $J=7.5\text{Hz}$), 6.98 (1H, t, $J=7.5\text{Hz}$), 7.17 (1H, t, $J=7.5\text{Hz}$), 7.25 (1H, d, $J=7.5\text{Hz}$), 7.97 (1H, s), 8.00 (2H, s)

30

MASS (m/z) : 378 (M^++1), 76 (bp)

(5) 3-Isobutyryl-1-(2-methoxybenzyl)-2-propylindole-6-carboxylic acid

35

mp : 190-191°C

BAD ORIGINAL

- 114 -

IR (KBr) : 1685, 1650, 1250 cm^{-1}

NMR (CDCl_3 , δ) : 1.03 (3H, t, $J=7\text{Hz}$), 1.30 (6H, d, $J=7\text{Hz}$), 1.58-1.68 (2H, m), 3.07-3.13 (2H, m), 3.54-3.63 (1H, m), 3.98 (3H, s), 5.45 (2H, s), 6.30 (1H, d, $J=7.5\text{Hz}$), 6.75 (1H, t, $J=7.5\text{Hz}$), 6.94 (1H, d, $J=7.5\text{Hz}$), 7.24 (1H, t, $J=7.5\text{Hz}$), 7.94-8.02 (2H, m), 8.05 (1H, s)

MASS (m/z) : 394 (M^++1), 76 (bp)

10 (6) 1-(2-Cyanobenzyl)-3-isobutyryl-2-propylindole-6-carboxylic acid

mp : 213.5-215°C

IR (KBr) : 2220, 1717 cm^{-1}

15 NMR (CDCl_3 , δ) : 1.04 (3H, t, $J=7\text{Hz}$), 1.31 (6H, d, $J=7\text{Hz}$), 1.53-1.67 (2H, m), 3.04-3.09 (2H, m), 3.52-3.62 (1H, m), 5.69 (2H, s), 6.47-6.50 (1H, m), 7.39-7.44 (2H, m), 7.77-7.80 (1H, m), 7.99-8.04 (3H, m)

MASS (m/z) : 389 (M^+-1), 76 (bp)

20

(7) 3-Isobutyryl-1-(2-nitrobenzyl)-2-propylindole-6-carboxylic acid

mp : 214-215°C

IR (KBr) : 1695, 1655, 1545 cm^{-1}

25 NMR (CDCl_3 , δ) : 1.02 (3H, t, $J=7\text{Hz}$), 1.32 (6H, d, $J=7\text{Hz}$), 1.57-1.65 (2H, m), 3.03 (2H, t, $J=7\text{Hz}$), 3.54-3.63 (1H, m), 5.89 (2H, s), 6.28 (1H, d, $J=7.5\text{Hz}$), 7.39-7.51 (2H, m), 7.92 (1H, s), 8.02 (2H, s), 8.30 (1H, d, $J=7.5\text{Hz}$)

30 MASS (m/z) : 409 (M^++1)

(8) 1-(2,6-Dichlorobenzyl)-3-isobutyryl-2-propylindole-6-carboxylic acid

mp : 241.5-243°C (dec.)

35 IR (KBr) : 1675, 1650 cm^{-1} BAD ORIGINAL 

- 115 -

NMR (CDCl₃, δ) : 0.99 (3H, t, J=7Hz), 1.28 (6H, d, J=7Hz), 1.39-1.52 (2H, m), 3.17-3.22 (2H, m), 3.50-3.59 (1H, m), 5.71 (2H, s), 7.24-7.28 (1H, m), 7.37-7.40 (2H, m), 7.94 (2H, q, J=7.5Hz), 8.10 (1H, s)

MASS (m/z) : 432 (M⁺+1), 76 (bp)

(9) 1-(2-Chloro-4-fluorobenzyl)-3-isobutyryl-2-propylindole-6-carboxylic acid

mp : 243-244°C

IR (KBr) : 1676, 1648, 1491 cm⁻¹

NMR (CDCl₃, δ) : 1.03 (3H, t, J=7Hz), 1.30 (6H, d, J=7Hz), 1.60 (2H, sextet, J=7Hz), 3.01-3.07 (2H, m), 3.53-3.62 (1H, m), 5.49 (2H, s), 6.20-6.26 (1H, m), 6.79 (1H, ddd, J=7.5, 7.5, 1Hz), 7.23 (1H, dd, J=7.5, 1Hz), 7.96 (1H, s), 7.99 (1H, d, J=7.5Hz)

MASS (m/z) : 414 (M⁺-1)

(10) 1-(4-Bromo-2-fluorobenzyl)-3-isobutyryl-2-propylindole-6-carboxylic acid

mp : 210-211°C

IR (KBr) : 1677, 1646, 1486 cm⁻¹

NMR (CDCl₃, δ) : 1.04 (3H, t, J=7Hz), 1.30 (6H, d, J=7Hz), 1.55-1.67 (2H, m), 3.07-3.12 (2H, m), 3.52-3.60 (1H, m), 5.46 (2H, s), 6.32 (1H, t, J=7.5Hz), 7.11 (1H, d, J=7.5Hz), 7.35 (1H, d, J=7.5Hz), 7.96-8.03 (3H, m)

MASS (m/z) : 460 (M⁺), 458 (M⁺-2)

(11) 3-Benzoyl-1-(2-chlorobenzyl)-2-propylindole-6-carboxylic acid

NMR (DMSO-d₆, δ) : 0.95 (3H, t, J=8Hz), 1.66 (2H, sextet, J=8Hz), 2.98 (2H, t, J=8Hz), 5.55 (2H, s), 6.35 (1H, dd, J=1, 8Hz), 7.09 (1H, dt, J=1, 8Hz), 7.20-7.27 (2H, m), 7.48 (1H, t, J=8Hz), 7.57-7.62

- 116 -

(1H, m), 7.72-7.82 (3H, m), 7.98 (1H, s)

(12) 1-(2-Chlorobenzyl)-3-cyano-2-propylindole-6-carboxylic acid

5 mp : 239.5-241°C

IR (KBr) : 2224, 1671, 1287, 1264 cm⁻¹

NMR (CDCl₃, δ) : 1.00 (3H, t, J=7Hz), 1.70 (2H, sextet, J=7Hz), 2.89 (2H, t, J=7Hz), 5.50 (2H, s), 6.25 (1H, d, J=7.5Hz), 7.18 (1H, ddt, J=7.5, 7.5, 1Hz), 7.25 (1H, ddd, J=7.5, 7.5, 1Hz), 7.47 (1H, d, J=7.5Hz), 7.78 (1H, dd, J=7.5, 1Hz), 7.99 (1H, d, J=1Hz), 8.01 (1H, d, J=7.5Hz)

MASS (m/z) : 351 (M⁺-1)

15 (13) 1-(2-Chlorobenzyl)-2-ethyl-3-isobutyrylindole-6-carboxylic acid

NMR (CDCl₃, δ) : 1.22 (3H, t, J=7Hz), 1.31 (6H, d, J=7Hz), 3.12 (2H, q, J=7Hz), 3.57 (1H, m), 5.51 (2H, s), 6.23 (1H, d, J=8Hz), 7.04 (1H, t, J=8Hz), 7.22 (1H, t, J=8Hz), 7.47 (1H, d, J=8Hz), 7.95-8.05 (3H, m)

(14) 1-(2-Chlorobenzyl)-3-isobutyryl-2-methylindole-6-carboxylic acid

25 NMR (CDCl₃, δ) : 1.31 (6H, d, J=7Hz), 2.72 (3H, s), 3.56 (1H, m), 5.51 (2H, s), 6.25 (1H, d, J=8Hz), 7.05 (1H, t, J=8Hz), 7.23 (1H, t, J=8Hz), 7.46 (1H, d, J=8Hz), 8.05 (3H, s)

30 (15) 1-(2-Chlorobenzyl)-3-isobutyryl-2-methoxymethylindole-6-carboxylic acid

NMR (CDCl₃, δ) : 1.32 (6H, d, J=7Hz), 3.35 (3H, s), 3.58 (1H, m), 4.94 (2H, s), 5.68 (2H, s), 6.28 (1H, d, J=8Hz), 7.03 (1H, t, J=8Hz), 7.20 (1H, t, J=8Hz), 7.45 (1H, d, J=8Hz), 8.0-8.05 (3H, m)

BAD ORIGINAL

- 117 -

(16) 1-(2-Chlorobenzyl)-3-isobutyrylindole-6-carboxylic acid

5 NMR (CDCl₃, δ) : 1.25 (6H, d, J=7Hz), 3.30 (1H, m),
5.52 (2H, s), 6.79 (1H, d, J=8Hz), 7.18 (1H, t,
J=8Hz), 7.28 (1H, t, J=8Hz), 7.47 (1H, d, J=8Hz),
7.91 (1H, s), 8.03 (1H, d, J=8Hz), 8.12 (1H, s),
8.48 (1H, d, J=8Hz)

(17) 3-Isobutyryl-2-propyl-1-(2-pyridylmethyl)indole-6-carboxylic acid

10 NMR (DMSO-d₆, δ) : 0.92 (3H, t, J=7Hz), 1.16 (6H, d,
J=7Hz), 1.46 (2H, sextet, J=7Hz), 3.12-3.17 (2H,
m), 3.52 (2H, septet, J=7Hz), 5.72 (2H, s), 7.16
(1H, d, J=8Hz), 7.29 (1H, dd, J=5, 8Hz), 7.76 (1H,
t, J=8Hz), 7.81 (1H, d, J=8Hz), 7.96 (1H, t,
15 J=8Hz), 8.06 (1H, s), 8.48 (1H, d, J=5Hz)

(18) 1-(2-Chlorobenzyl)-2,3-diethylindole-6-carboxylic acid

mp : 258-259°C (dec.)

IR (KBr) : 1675, 1290 cm⁻¹

20 NMR (CDCl₃, δ) : 1.14 (3H, t, J=7Hz), 1.30 (3H, t,
J=7Hz), 2.71 (2H, q, J=7Hz), 2.80 (2H, q, J=7Hz),
5.45 (2H, s), 6.18 (1H, d, J=7.5Hz), 7.00 (1H, t,
J=7.5Hz), 7.19 (1H, t, J=7.5Hz), 7.42 (1H, d,
J=7.5Hz), 7.62 (1H, d, J=7.5Hz), 7.84 (1H, d,
25 J=7.5Hz), 7.91 (1H, s)

MASS (m/z) 340 (M⁺-1)

(19) 1-(2-Chlorobenzyl)-3-formyl-2-propylindole-6-carboxylic acid

30 NMR (CDCl₃, δ) : 1.01 (3H, t, J=7Hz), 1.67 (2H, m),
3.03 (2H, t, J=7Hz), 5.50 (2H, s), 6.40 (1H, d,
J=8Hz), 7.08 (1H, t, J=8Hz), 7.24 (1H, t, J=8Hz),
7.48 (1H, d, J=8Hz), 7.98 (1H, s), 8.07 (1H, d,
J=8Hz), 8.40 (1H, d, J=8Hz)

35

BAD ORIGINAL

- 118 -

(20) (2-Chlorobenzyl)-3-phenylacetyl-2-propylindole-6-carboxylic acid

5 NMR (DMSO- d_6 , δ) : 0.90 (3H, t, J=8Hz), 1.45 (2H, sextet, J=8Hz), 3.04-3.08 (2H, m), 4.43 (2H, s), 5.68 (2H, s), 6.27 (1H, d, J=8Hz), 7.18 (1H, t, J=8Hz), 7.23-7.35 (6H, m), 7.58 (1H, d, J=8Hz), 7.85 (1H, d, J=8Hz), 7.96 (1H, s), 8.19 (1H, d, J=8Hz)

10 (21) 3-Acetyl-1-(6-chloro-3,4-methylenedioxybenzyl)-2-propylindole-6-carboxylic acid

mp : 238-239°C

15 NMR (CDCl₃-CD₃OD = 1:1, δ) : 1.06 (3H, t, J=8Hz), 1.65 (2H, sextet, J=8Hz), 2.76 (3H, s), 3.08-3.14 (2H, m), 5.48 (2H, s), 5.74 (1H, s), 5.92 (2H, s), 6.96 (1H, s), 7.99 (1H, d, J=8Hz), 8.02 (1H, s), 8.08 (1H, d, J=8Hz)

Example 35

20 Methyl 3-acetyl-1-(2-chlorobenzyl)-2-ethylindole-6-carboxylate (170 mg) was prepared from methyl 3-acetyl-2-ethylindole-6-carboxylate (100 mg) and 2-chlorobenzyl bromide (0.06 ml) in a similar manner to that of Example 1.

25 This product was used immediately without purification in the below-mentioned Example 36.

Example 36

30 3-Acetyl-1-(2-chlorobenzyl)-2-ethylindole-6-carboxylic acid (137 mg) was prepared from methyl 3-acetyl-1-(2-chlorobenzyl)-2-ethylindole-6-carboxylate (170 mg) in a similar manner to that of Example 2.

35 NMR (DMSO- d_6 , δ) : 1.11 (3H, t, J=7Hz), 2.67 (3H, s), 3.11 (2H, q, J=7Hz), 5.68 (2H, s), 6.26 (1H, d, J=8Hz), 7.19 (1H, t, J=8Hz), 7.32 (1H, t, J=8Hz),

BAD ORIGINAL

- 119 -

7.58 (1H, d, J=8Hz), 7.83 (1H, d, J=8Hz), 7.94 (1H, s), 8.13 (1H, d, J=8Hz)

Example 37

5 The following compounds described in 1) to 19) were prepared from the compound (I-2) obtained in Example 34 and Example 36 in a similar manner to that of Example 3.

10 (1) 1-(2-Fluorobenzyl)-3-isobutyryl-2-propylindole-6-carboxamide
mp : 198°C
IR (KBr) : 3200, 1650, 1610 cm^{-1}
NMR (CDCl_3 , δ) : 1.03 (3H, t, J=7Hz), 1.30 (6H, d, J=7Hz), 1.55-1.64 (2H, m), 3.06-3.12 (2H, m), 3.50-3.60 (1H, m), 5.50 (2H, s), 6.42 (1H, t, J=7.5Hz), 6.95 (2H, t, J=7.5Hz), 7.09-7.17 (1H, m), 7.22-7.28 (1H, m), 7.61 (1H, t, J=7.5Hz), 7.90 (1H, s), 7.96 (1H, t, J=7.5Hz)
MASS (m/z) : 381 ($\text{M}^+ + 1$)

20 (2) 1-(2-Bromobenzyl)-3-isobutyryl-2-propylindole-6-carboxamide
mp : 173-174°C
IR (KBr) : 3400, 1660, 1630 cm^{-1}
25 NMR (CDCl_3 , δ) : 1.03 (3H, t, J=7Hz), 1.30 (6H, d, J=7Hz), 1.57-1.68 (2H, m), 3.00-3.06 (2H, m), 3.51-3.61 (1H, m), 5.46 (2H, s), 6.20 (1H, t, J=7.5Hz), 7.05-7.18 (2H, m), 7.60-7.66 (1H, m), 7.83 (1H, s), 7.99 (1H, t, J=7.5Hz)
30 MASS (m/z) : 443 ($\text{M}^+ + 2$), 441 (M^+), 76 (bp)

(3) 1-(2-Iodobenzyl)-3-isobutyryl-2-propylindole-6-carboxamide
mp : 186-187°C
35 IR (KBr) : 3400, 1665, 1640 cm^{-1}

- 120 -

5 NMR (CDCl₃, δ) : 1.03 (3H, t, J=7Hz), 1.30 (6H, d, J=7Hz), 1.54-1.67 (2H, m), 2.99-3.05 (2H, m), 3.51-3.60 (1H, m), 5.39 (2H, s), 6.15 (1H, d, J=7.5Hz), 6.99 (1H, t, J=7.5Hz), 7.11 (1H, t, J=7.5Hz), 7.64 (1H, d, J=7.5Hz), 7.82 (1H, s), 7.92 (1H, d, J=7Hz), 7.99 (1H, d, J=7Hz)
MASS (m/z) : 489 (M⁺+1), 76 (bp)

10 (4) 3-Isobutyryl-1-(2-methylbenzyl)-2-propylindole-6-carboxamide
mp : 190-191°C
IR (KBr) : 3395, 1650, 1625, 1410 cm⁻¹
15 NMR (CDCl₃, δ) : 1.00 (3H, t, J=7Hz), 1.31 (6H, d, J=7Hz), 1.54-1.68 (2H, m), 2.49 (3H, s), 3.00-3.07 (2H, m), 3.52-3.61 (1H, m), 5.38 (2H, s), 6.14 (1H, d, J=7.5Hz), 6.98 (1H, t, J=7.5Hz), 7.17 (1H, t, J=7.5Hz), 7.24 (1H, d, J=7.5Hz), 7.60 (1H, d, J=7.5Hz), 7.82 (1H, s), 7.99 (1H, d, J=7.5Hz)
MASS (m/z) : 377 (M⁺+1), 76 (bp)

20 (5) 3-Isobutyryl-1-(2-methoxybenzyl)-2-propylindole-6-carboxamide
mp : 174-175°C
IR (KBr) : 3370, 1655, 1650, 1625 cm⁻¹
25 NMR (CDCl₃, δ) : 1.01 (3H, t, J=7Hz), 1.30 (6H, d, J=7Hz), 1.57-1.69 (2H, m), 3.05-3.10 (2H, m), 3.52-3.61 (1H, m), 3.97 (3H, s), 5.43 (2H, s), 6.24 (1H, d, J=7.5Hz), 6.74 (2H, t, J=7.5Hz), 6.93 (1H, d, J=7.5Hz), 7.24 (1H, t, J=7.5Hz), 7.59 (1H, d, J=7.5Hz), 7.88 (1H, s), 7.97 (1H, d, J=7.5Hz)
30 MASS (m/z) : 393 (M⁺+1), 76 (bp)

35 (6) 1-(2-Cyanobenzyl)-3-isobutyryl-2-propylindole-6-carboxamide
mp : 143-144°C

BAD ORIGINAL

- 121 -

IR (KBr) : 3377, 3190, 2227, 1645 cm^{-1}

NMR (CDCl_3 , δ) : 1.04 (3H, t, $J=7\text{Hz}$), 1.30 (6H, d, $J=7\text{Hz}$), 1.52-1.65 (2H, m), 3.02-3.08 (2H, m), 3.50-3.59 (1H, m), 5.68 (2H, s), 6.45-6.49 (1H, m), 7.38-7.43 (2H, m), 7.65 (1H, d, $J=7.5\text{Hz}$), 7.74-7.78 (1H, m), 7.87 (1H, s), 7.99 (1H, d, $J=7.5\text{Hz}$)

MASS (m/z) : 388 (M^++1), 62 (bp)

(7) 3-Isobutyryl-1-(2-nitrobenzyl)-2-propylindole-6-carboxamide

mp : 181-182°C

IR (KBr) : 3190, 1670, 1610, 1535, 1400 cm^{-1}

NMR (CDCl_3 , δ) : 1.00 (3H, t, $J=7\text{Hz}$), 1.32 (6H, d, $J=7\text{Hz}$), 1.56-1.67 (2H, m), 3.02 (2H, t, $J=7\text{Hz}$), 3.52-3.61 (1H, m), 5.89 (2H, s), 6.27 (1H, d, $J=7.5\text{Hz}$), 7.39-7.50 (2H, m), 7.63 (1H, d, $J=7.5\text{Hz}$), 7.80 (1H, s), 7.99 (1H, d, $J=7.5\text{Hz}$), 8.28 (1H, d, $J=7.5\text{Hz}$)

MASS (m/z) : 408 (M^++1), 76 (bp)

(8) 1-(2,6-Dichlorobenzyl)-3-isobutyryl-2-propylindole-6-carboxamide

mp : 207.5-209°C

IR (KBr) : 3395, 1650, 1615 cm^{-1}

NMR (CDCl_3 , δ) : 0.98 (3H, t, $J=7\text{Hz}$), 1.28 (6H, d, $J=7\text{Hz}$), 1.39-1.50 (2H, m), 3.16-3.21 (2H, m), 3.49-3.58 (1H, m), 5.70 (2H, s), 7.22-7.25 (1H, m), 7.35-7.39 (2H, m), 7.60 (1H, d, $J=7.5\text{Hz}$), 7.86-7.90 (2H, m), 7.99 (1H, d, $J=7.5\text{Hz}$)

MASS (m/z) : 431 (M^++1), 76 (bp)

(9) 1-(2-Chloro-4-fluorobenzyl)-3-isobutyryl-2-propylindole-6-carboxamide

mp : 192-193°C

IR (KBr) : 3336, 3180, 1650, 1494, 1411 cm^{-1} BAD ORIGINAL 

- 122 -

5 NMR (CDCl₃, δ) : 1.03 (3H, t, J=7Hz), 1.30 (6H, d, J=7Hz), 1.53-1.65 (2H, m), 3.01-3.07 (2H, m), 3.50-3.60 (1H, m), 5.47 (2H, s), 6.20 (1H, dd, J=8, 7.5Hz), 6.78 (1H, ddd, J=7.5, 7.5, 1Hz), 7.23 (1H, dd, J=8, 1Hz), 7.63 (1H, d, J=7.5Hz), 7.85 (1H, s), 7.99 (1H, d, J=8Hz)

MASS (m/z) : 415 (M⁺+1), 76 (bp)

10 (10) 1-(4-Bromo-2-fluorobenzyl)-3-isobutyryl-2-propylindole-6-carboxamide

mp : 197-198.5°C

IR (KBr) : 3377, 3189, 1652, 1617, 1487, 1408 cm⁻¹

15 NMR (CDCl₃, δ) : 1.04 (3H, t, J=7Hz), 1.30 (6H, d, J=7Hz), 1.53-1.64 (2H, m), 3.05-3.11 (2H, m), 3.48-3.60 (1H, m), 5.44 (2H, s), 6.29 (1H, t, J=7.5Hz), 7.09 (1H, d, J=7.5Hz), 7.33 (1H, dd, J=7.5, 1Hz), 7.62 (1H, d, J=7.5Hz), 7.90 (1H, d, J=1Hz), 7.97 (1H, d, J=7.5Hz)

MASS (m/z) : 461 (M⁺+2), 459 (M⁺), 76 (bp)

20

(11) 1-(2-Chlorobenzyl)-3-cyano-2-propylindole-6-carboxamide

mp : 222-223.5°C

IR (KBr) : 3443, 3183, 2215, 1679, 1394 cm⁻¹

25 NMR (CDCl₃, δ) : 1.02 (3H, t, J=7Hz), 1.70 (2H, sextet, J=7Hz), 2.89 (2H, t, J=7.5Hz), 5.50 (2H, s), 6.21 (1H, d, J=7.5Hz), 7.08 (1H, t, J=7.5Hz), 7.24 (1H, ddd, J=7.5, 7.5, 1Hz), 7.47 (1H, d, J=7.5Hz), 7.61 (1H, d, J=7.5Hz), 7.77 (1H, d, J=7.5Hz), 7.89 (1H, d, J=1Hz)

30 MASS (m/z) : 352 (M⁺+1), 76 (bp)

(12) 1-(2-Chlorobenzyl)-2-ethyl-3-isobutyrylindole-6-carboxamide

mp : 178-180.5°C

35 NMR (CDCl₃, δ) : 1.22 (3H, t, J=7Hz), 1.30 (6H, d,

BAD ORIGINAL 

- 123 -

J=7Hz), 3.09 (2H, q, J=7Hz), 3.56 (1H, m), 5.51 (2H, s), 6.22 (1H, d, J=8Hz), 7.04 (1H, t, J=8Hz), 7.22 (1H, t, J=8Hz), 7.44 (1H, d, J=8Hz), 7.63 (1H, d, J=8Hz), 7.82 (1H, s), 7.98 (1H, d, J=8Hz)

5

(13) 1-(2-Chlorobenzyl)-3-isobutyryl-2-methylindole-6-carboxamide

mp : 212-215°C

10 NMR (CDCl₃, δ) : 1.30 (6H, d, J=7Hz), 2.69 (3H, s), 3.53 (1H, m), 5.48 (2H, s), 6.21 (1H, d, J=8Hz), 7.04 (1H, t, J=8Hz), 7.23 (1H, t, J=8Hz), 7.45 (1H, d, J=8Hz), 7.62 (1H, d, J=8Hz), 7.87 (1H, s), 8.03 (1H, d, J=8Hz)

15 (14) 1-(2-Chlorobenzyl)-3-isobutyryl-2-methoxymethylindole-6-carboxamide

mp : 204-206°C

20 NMR (CDCl₃, δ) : 1.32 (6H, d, J=7Hz), 3.34 (3H, s), 3.57 (1H, m), 4.92 (2H, s), 5.65 (2H, s), 6.24 (1H, d, J=8Hz), 7.03 (1H, t, J=8Hz), 7.21 (1H, t, J=8Hz), 7.44 (1H, d, J=8Hz), 7.67 (1H, d, J=8Hz), 7.83 (1H, s), 8.02 (1H, d, J=8Hz)

(15) 1-(2-Chlorobenzyl)-3-isobutyrylindole-6-carboxamide

25 mp : 235-237°C

30 NMR (DMSO-d₆, δ) : 1.16 (6H, d, J=7Hz), 3.40 (1H, m), 5.67 (2H, s), 6.70 (1H, d, J=8Hz), 7.2-7.4 (3H, m), 7.56 (1H, d, J=8Hz), 7.80 (1H, d, J=8Hz), 7.96 (1H, br s), 8.04 (1H, s), 8.27 (1H, d, J=8Hz), 8.64 (1H, s)

(16) 3-Isobutyryl-2-propyl-1-(2-pyridylmethyl)indole-6-carboxamide

35 NMR (DMSO-d₆, δ) : 0.90 (3H, t, J=7Hz), 1.17 (6H, d, J=7Hz), 1.46 (2H, sextet, J=7Hz), 3.06-3.15 (2H,

- 124 -

m), 3.52 (2H, septet, $J=7\text{Hz}$), 5.66 (2H, s), 7.08 (1H, d, $J=8\text{Hz}$), 7.28-7.32 (2H, m), 7.78 (1H, d, $J=8\text{Hz}$), 7.92 (1H, d, $J=8\text{Hz}$), 8.09 (1H, s), 8.50 (1H, d, $J=5\text{Hz}$)

5

(17) 1-(2-Chlorobenzyl)-2,3-diethylindole-6-carboxamide

mp : 185-187.5°C

IR (KBr) : 3400, 1650, 1610 cm^{-1}

10

NMR (CDCl_3 , δ) : 1.15 (3H, t, $J=7\text{Hz}$), 1.29 (3H, t, $J=7\text{Hz}$), 2.69 (2H, q, $J=7\text{Hz}$), 2.80 (2H, q, $J=7\text{Hz}$), 5.44 (2H, s), 6.17 (1H, d, $J=7.5\text{Hz}$), 7.00 (1H, t, $J=7.5\text{Hz}$), 7.18 (1H, t, $J=7.5\text{Hz}$), 7.41 (1H, d, $J=7.5\text{Hz}$), 7.47 (1H, d, $J=7.5\text{Hz}$), 7.62 (1H, d, $J=7.5\text{Hz}$), 7.76 (1H, s)

15

MASS (m/z) : 341 (M^++1), 76 (bp)

(18) 3-Acetyl-1-(2-chlorobenzyl)-2-ethylindole-6-carboxamide

mp : 217-220°C

20

NMR (CDCl_3 , δ) : 1.22 (3H, t, $J=7\text{Hz}$), 2.73 (3H, s), 3.12 (2H, q, $J=7\text{Hz}$), 5.49 (2H, s), 6.20 (1H, d, $J=8\text{Hz}$), 7.02 (1H, t, $J=8\text{Hz}$), 7.22 (1H, t, $J=8\text{Hz}$), 7.43 (1H, d, $J=8\text{Hz}$), 7.63 (1H, d, $J=8\text{Hz}$), 7.83 (1H, s), 8.08 (1H, d, $J=8\text{Hz}$)

25

(19) 1-(2-Chlorobenzyl)-3-formyl-2-propylindole-6-carboxamide

mp : 245°C (dec.)

NMR ($\text{DMSO}-d_6$, δ) : 0.92 (3H, t, $J=7\text{Hz}$), 1.63 (2H, m), 3.11 (2H, t, $J=7\text{Hz}$), 5.64 (2H, s), 6.32 (1H, d, $J=8\text{Hz}$), 7.21 (1H, t, $J=8\text{Hz}$), 7.25-7.35 (2H, m), 7.60 (1H, d, $J=8\text{Hz}$), 7.83 (1H, d, $J=8\text{Hz}$), 7.95 (1H, d, $J=8\text{Hz}$), 7.97 (1H, s), 8.21 (1H, d, $J=8\text{Hz}$), >10 (1H, s)

30

Example 38

35

The following compounds described in 1) to 3) were

BAD ORIGINAL

- 125 -

prepared from the compound (I-2) obtained in Example 34-11), Example 34-20) or Example 34-21) in a similar manner to that of Example 6.

5 (1) 3-Benzoyl-1-(2-chlorobenzyl)-2-propylindole-6-carboxamide

NMR (DMSO-d₆, δ) : 0.78 (3H, t, J=8Hz), 1.46 (2H, sextet, J=8Hz), 2.88 (2H, t, J=8Hz), 5.66 (2H, s), 6.33 (1H, dd, J=1, 8Hz), 7.08 (1H, dt, J=1, 8Hz),
10 7.20-7.38 (3H, m), 7.52-7.72 (7H, m), 7.88 (1H, br s), 7.99 (1H, s)

(2) 1-(2-Chlorobenzyl)-3-phenylacetyl-2-propylindole-6-carboxamide

15 NMR (DMSO-d₆, δ) : 0.88 (3H, t, J=8Hz), 1.47 (2H, sextet, J=8Hz), 2.98-3.03 (2H, m), 4.42 (2H, s), 5.63 (2H, s), 6.20 (1H, d, J=8Hz), 7.17 (1H, t, J=8Hz), 7.24-7.35 (6H, m), 7.57 (1H, d, J=8Hz), 7.82 (1H, d, J=8Hz), 7.95 (1H, br s), 8.02 (1H, s),
20 8.14 (1H, d, J=8Hz)

(3) 3-Acetyl-1-(6-chloro-3,4-methylenedioxybenzyl)-2-propylindole-6-carboxamide

mp : 220-223°C
25 NMR (DMSO-d₆, δ) : 0.94 (3H, t, J=8Hz), 1.50 (2H, sextet, J=8Hz), 2.65 (3H, s), 3.02-3.06 (2H, m), 5.52 (2H, s), 5.66 (1H, s), 5.99 (2H, s), 7.23 (1H, s), 7.86 (1H, d, J=8Hz), 8.01 (1H, s), 8.05 (1H, d, J=8Hz)

30

Example 39

To a solution of 3-isobutyryl-2-propyl-1-(2-pyridylmethyl)indole-6-carboxamide (80 mg) in chloroform (2 ml) was added 1M solution of hydrogen chloride in methanol (1
35 ml) at 25°C, and the mixture was stirred for 15 minutes.

- 126 -

After evaporation of solvent, the residue was crystallized from a mixture of ethanol and ethyl acetate to give 3-isobutyryl-2-propyl-1-(2-pyridylmethyl)indole-6-carboxamide hydrochloride (80 mg) as colorless crystals.

5 mp : 230-235°C

NMR (DMSO-d₆, δ) : 0.92 (3H, t, J=7Hz), 1.17 (6H, d, J=7Hz), 1.45 (2H, sextet, J=7Hz), 3.08-3.14 (2H, m), 3.52 (2H, septet, J=7Hz), 5.74 (2H, s), 7.09 (1H, d, J=8Hz), 7.46 (1H, dd, J=5, 8Hz), 7.79 (1H, d, J=8Hz), 7.90 (1H, d, J=8Hz) 7.92 (1H, t, J=8Hz), 8.12 (1H, s), 8.62 (1H, d, J=5Hz)

10

Example 40

1-(2-Carboxybenzyl)-3-isobutyryl-2-propylindole-6-carboxamide (242 mg) was prepared from 3-isobutyryl-1-(2-methoxycarbonylbenzyl)-2-propylindole-6-carboxamide (265 mg) in a similar manner to that of Example 2.

15

mp : 268-269°C (dec.)

IR (KBr) : 1740, 1690, 1625, 1620 cm⁻¹

20 NMR (DMSO-d₆, δ) : 0.90 (3H, t, J=7Hz), 1.19 (6H, d, J=7Hz), 1.42-1.51 (2H, m), 2.94-3.06 (2H, m), 3.50-3.60 (1H, m), 5.96 (2H, s), 6.06-6.10 (1H, m), 7.37-7.40 (2H, m), 7.79-7.82 (1H, m), 7.91-7.95 (1H, m), 7.99 (1H, s), 8.03-8.06 (1H, m)

25 MASS (m/z) : 407 (M⁺+1), 86 (bp)

Example 41

1-(2-Carbamoylbenzyl)-3-isobutyryl-2-propylindole-6-carboxamide (102 mg) was prepared from 1-(2-carboxybenzyl)-3-isobutyryl-2-propylindole-6-carboxamide (164 mg) in a similar manner to that of Example 3.

30

mp : 273-274°C

IR (KBr) : 1690 cm⁻¹

35 NMR (DMSO-d₆, δ) : 0.91 (3H, t, J=7Hz), 1.19 (6H, d, J=7Hz), 1.41-1.51 (2H, m), 2.94-2.99 (2H, m), 3.48-

BAD ORIGINAL

- 127 -

3.57 (1H, m), 5.79 (2H, s), 6.17 (1H, d, J=7.5Hz),
7.22-7.35 (3H, m), 7.61-7.68 (2H, m), 7.80 (1H, d,
J=7.5Hz), 7.92-7.97 (2H, m), 8.04 (1H, s), 8.13
(1H, s)

5 MASS (m/z) : 406 ($M^+ + 1$), 87 (bp)

Example 42

To a solution of phosphorus oxychloride (0.031 ml) in
dimethylformamide (1.2 ml) was added 1-(2-chlorobenzyl)-2-
10 ethyl-3-propionylindole-6-carboxamide (112 mg) at 0°C, and
the mixture was stirred for 15 minutes. The resulting
mixture was poured into ammonia water and ice, and then
extracted with ethyl acetate. The organic phase was washed
with brine, dried over sodium sulfate and evaporated in
15 vacuo. The residue was triturated with a mixture of hexane
and isopropyl ether to give 1-(2-chlorobenzyl)-2-ethyl-3-
propionylindole-6-carbonitrile (93 mg) as a solid.

mp : 115-118°C

20 NMR (CDCl₃, δ) : 1.25 (3H, t, J=7Hz), 1.30 (3H, t,
J=7Hz), 3.09 (2H, q, J=7Hz), 3.17 (2H, q, J=7Hz),
5.47 (2H, s), 6.21 (1H, d, J=8Hz), 7.07 (1H, t,
J=8Hz), 7.25 (1H, t, J=8Hz), 7.45-7.55 (3H, m),
8.09 (1H, d, J=7Hz)

25 Example 43

1-(2-Chlorobenzyl)-2-ethyl-3-isobutyrylindole-6-
carbonitrile (239 mg) was prepared from 1-(2-chlorobenzyl)-2-
ethyl-3-isobutyrylindole-6-carboxamide (280 mg) in a similar
manner to that of Example 42.

30 mp : 132-134°C

35 NMR (CDCl₃, δ) : 1.23 (3H, t, J=7Hz), 1.31 (6H, d,
J=7Hz), 3.13 (2H, q, J=7Hz), 3.50 (1H, m), 5.48
(2H, s), 6.22 (1H, d, J=8Hz), 7.07 (1H, t, J=8Hz),
7.27 (1H, t, J=8Hz), 7.27 (1H, d, J=8Hz), 7.44-7.53
(2H, m), 8.02 (1H, d, J=8Hz)

- 128 -

Example 44

To a solution of 1-(2-chlorobenzyl)-2-ethyl-3-propionylindole-6-carbonitrile (107 mg) in xylene (5 ml) was added trimethyltin azide (190 mg), and the mixture was stirred at 120°C for 14 hours. The resulting mixture was poured into 1N HCl and extracted with ethyl acetate. The organic phase was washed with brine, dried over sodium sulfate and evaporated in vacuo. The residue was chromatographed on silica gel eluting with 20% methanol in chloroform to give 1-(2-chlorobenzyl)-2-ethyl-3-propionyl-6-(1H-tetrazol-5-yl)indole (77 mg) as a solid.

mp : 178-181°C

NMR (CDCl₃, δ) : 1.18 (3H, t, J=7Hz), 1.34 (3H, t, J=7Hz), 3.0-3.15 (4H, m), 5.42 (2H, s), 6.21 (1H, d, J=8Hz), 6.94 (1H, t, J=8Hz), 7.13 (1H, t, J=8Hz), 7.33 (1H, d, J=8Hz), 8.03 (1H, d, J=8Hz), 8.05 (1H, s), 8.25 (1H, d, J=8Hz)

Example 45

1-(2-Chlorobenzyl)-2-ethyl-3-isobutyryl-6-(1H-tetrazol-5-yl)indole (109 mg) was prepared from 1-(2-chlorobenzyl)-2-ethyl-3-isobutyrylindole-6-carbonitrile (130 mg) in a similar manner to that of Example 44.

mp : 160-163°C

NMR (CDCl₃, δ) : 1.18 (3H, t, J=7Hz), 1.31 (6H, d, J=7Hz), 3.04 (2H, q, J=7Hz), 3.52 (1H, m), 5.37 (2H, s), 6.20 (1H, d, J=8Hz), 6.94 (1H, t, J=8Hz), 7.11 (1H, t, J=8Hz), 7.33 (1H, d, J=8Hz), 8.00 (1H, d, J=8Hz), 8.02 (1H, s), 8.13 (1H, d, J=8Hz)

Example 46

The following compounds described in (1) to (2) were prepared in a similar manner to that of Preparation 30.

(1) Methyl 2-(3-carboxypropyl)-1-(2-chlorobenzyl)indole-6-

BAD ORIGINAL

- 129 -

carboxylate

5 NMR (CDCl₃, δ) : 2.04 (2H, m), 2.45 (2H, t, J=7Hz),
2.73 (2H, t, J=7Hz), 3.89 (3H, s), 5.44 (2H, s),
6.14 (1H, d, J=8Hz), 6.47 (1H, s), 7.01 (1H, t,
J=8Hz), 7.18 (1H, t, J=8Hz), 7.44 (1H, d, J=8Hz),
7.62 (1H, d, J=8Hz), 7.83 (1H, d, J=8Hz), 7.93 (1H,
s)

10 (2) 2-(2-Carboxyethyl)-1-(2-chlorobenzyl)indole-6-
carboxylate

15 NMR (CDCl₃, δ) : 2.76 (2H, t, J=7Hz), 2.96 (2H, t,
J=7Hz), 3.88 (3H, s), 5.46 (2H, s), 6.16 (1H, d,
J=8Hz), 6.46 (1H, s), 7.01 (1H, t, J=8Hz), 7.20
(1H, t, J=8Hz), 7.43 (1H, d, J=8Hz), 7.62 (1H, d,
J=8Hz), 7.82 (1H, d, J=8Hz), 7.93 (1H, s)

Preparation 47

The following compounds described in (1) to (2) were
prepared in a similar manner to that of Preparation 31.

20

(1) Methyl 9-(2-chlorobenzyl)-5-oxo-5,6,7,8-
tetrahydrocarbazole-2-carboxylate

25 NMR (CDCl₃, δ) : 2.24 (2H, m), 2.62 (2H, t, J=7Hz),
2.86 (2H, t, J=7Hz), 3.90 (3H, s), 5.47 (2H, s),
6.34 (1H, d, J=8Hz), 7.09 (1H, t, J=8Hz), 7.25 (1H,
t, J=8Hz), 7.47 (1H, d, J=8Hz), 7.97 (1H, s), 7.99
(1H, d, J=8Hz), 8.33 (1H, d, J=8Hz)

30 (2) Methyl 4-(2-chlorobenzyl)-1-oxo-1,2,3,4-
tetrahydrocyclopent[b]indole-6-carboxylate

NMR (CDCl₃, δ) : 2.9-3.15 (4H, m), 3.91 (3H, s), 5.46
(2H, s), 6.66 (1H, d, J=8Hz), 7.17 (1H, t, J=8Hz),
7.29 (1H, t, J=8Hz), 7.48 (1H, d, J=8Hz), 7.94-8.06
(3H, m)

35

BAD ORIGINAL

- 130 -

Example 48

The following compounds described in (1) to (2) were prepared in a similar manner to that of Preparation 1 (5).

- 5 (1) Methyl 3-chloroacetyl-1-(2-chlorobenzyl)-2-propylindole-6-carboxylate

mp : 143-145°C

IR (KBr) : 1722, 1666 cm^{-1}

10 NMR (CDCl_3 , δ) : 1.03 (3H, t, $J=7\text{Hz}$), 1.55-1.66 (2H, m), 3.05-3.10 (2H, m), 3.91 (3H, s), 4.82 (2H, s), 5.53 (2H, s), 6.25 (1H, d, $J=7.5\text{Hz}$), 7.05 (1H, t, $J=7.5\text{Hz}$), 7.20-7.25 (1H, m), 7.49 (1H, d, $J=7.5\text{Hz}$), 7.88 (1H, d, $J=8\text{Hz}$), 7.96 (1H, s), 8.00 (1H, d, $J=8\text{Hz}$)

15 MASS (m/z) : 418 (M^+-1), 76 (bp)

- (2) 1-(2-Chlorobenzyl)-3-crotonoyl-2-propylindole-6-carboxamide

mp : 185.5-186.5°C

20 IR (KBr) : 1648, 1614, 1443, 1414, 1388 cm^{-1}

NMR (CDCl_3 , δ) : 1.00 (3H, t, $J=7\text{Hz}$), 1.64 (2H, sextet, $J=7\text{Hz}$), 2.04 (3H, d, $J=7\text{Hz}$), 3.00 (2H, t, $J=7\text{Hz}$), 5.51 (2H, s), 6.24 (1H, d, $J=8\text{Hz}$), 6.92 (1H, d, $J=15\text{Hz}$), 7.00-7.06 (2H, m), 7.23 (1H, t, $J=8\text{Hz}$), 7.46 (1H, d, $J=7.5\text{Hz}$), 7.60 (1H, d, $J=7.5\text{Hz}$), 7.83 (1H, s), 7.99 (1H, d, $J=8\text{Hz}$)

25 MASS (m/z) : 395 (M^++1), 74 (bp)

Example 49

30 A mixture of methyl 3-chloroacetyl-1-(2-chlorobenzyl)-2-propylindole-6-carboxylate (123 mg) and morpholine (1 ml) was stirred at 50°C for 2.5 hours. After cooled to 20°C, the reaction mixture was extracted with ethyl acetate. The organic phase was washed with 1N hydrochloric acid and water, 35 dried over magnesium sulfate and evaporated in vacuo. The

- 131 -

residue was chromatographed on silica gel eluting with a mixture of ethyl acetate and hexane (1:2) to give methyl 1-(2-chlorobenzyl)-3-morpholinoacetyl-2-propylindole-6-carboxylate (94 mg) as colorless amorphous.

5 IR (KBr) : 1712, 1657 cm^{-1}

NMR (CDCl_3 , δ) : 1.01 (3H, t, $J=7\text{Hz}$), 1.60-1.65 (2H, m), 2.70-2.75 (4H, m), 3.06 (2H, t, $J=7\text{Hz}$), 3.84 (4H, t, $J=7\text{Hz}$), 3.90 (2H, s), 3.92 (3H, s), 5.52 (2H, s), 6.24 (1H, d, $J=7.5\text{Hz}$), 7.06 (1H, t, $J=7.5\text{Hz}$), 7.24 (1H, t, $J=7.5\text{Hz}$), 7.48 (1H, d, $J=7.5\text{Hz}$), 7.94-7.98 (3H, m)

10 MASS (m/z) : 469 ($M^+ + 1$)

Example 50

15 To a mixture of methyl 1-(2-chlorobenzyl)-3-formyl-2-propylindole-6-carboxylate (263 mg), 2-methyl-2-butene (220 mg) and sodium dihydrogenphosphate (128 mg) in a mixture of tert-butanol (7 ml) and water (1.3 ml) was added sodium chlorite (219 mg) at 20°C. The reaction mixture was stirred
20 at 40°C for 2 hours. The reaction mixture was acidified with 1N hydrochloric acid at 0°C and extracted with chloroform three times. The organic phase was dried over sodium sulfate and evaporated in vacuo. The residue was chromatographed on silica gel eluting with a mixture of ethyl acetate and hexane
25 (1:2) to give 1-(2-chlorobenzyl)-6-methoxycarbonyl-2-propylindole-3-carboxylic acid (94 mg) as pale yellow crystals.

mp : 229-231°C (dec.)

IR (KBr) : 1715, 1658, 1441, 1275, 1227 cm^{-1}

30 NMR (CDCl_3 , δ) : 1.05 (3H, t, $J=7\text{Hz}$), 1.60-1.70 (2H, m), 3.10-3.18 (2H, m), 3.93 (3H, s), 5.54 (2H, s), 6.78 (1H, d, $J=7.5\text{Hz}$), 7.06 (1H, t, $J=7.5\text{Hz}$), 7.21-7.25 (1H, m), 7.49 (1H, d, $J=7.5\text{Hz}$), 7.95 (1H, s), 7.99 (1H, d, $J=8\text{Hz}$), 8.33 (1H, d, $J=8\text{Hz}$)

35 MASS (m/z) : 384 ($M^+ - 1$), 77 (bp)

BAD ORIGINAL

- 132 -

Example 51

To a stirred suspension of 60% sodium hydride (470 mg) in N,N-dimethylformamide (6 ml) was added a solution of methyl 2-ethylindole-6-carboxylate (1.99 g) in N,N-dimethylformamide (12 ml) at 20°C. The mixture was stirred at 20°C for 30 minutes. To this mixture was added 2-chlorobenzylbromide (2.21 g) at 20°C and the mixture was stirred at 20°C for 5.5 hours. N,N-Dimethylformamide was evaporated off, and the residue was extracted with ethyl acetate. The organic phase was washed with water and brine, dried over sodium sulfate and evaporated in vacuo. The residue was chromatographed on silica gel eluting with a mixture of ethyl acetate and hexane (1:8) to give crystals which were washed with hexane to give methyl 1-(2-chlorobenzyl)-2-ethylindole-6-carboxylate (2.71 g) as colorless crystals.

mp : 87-89°C

IR (KBr) : 1709, 1278, 1236 cm⁻¹

NMR (CDCl₃, δ) : 1.35 (3H, t, J=7Hz), 2.67 (2H, q, J=7Hz), 3.91 (3H, s), 5.45 (2H, s), 6.17 (1H, d, J=7Hz), 6.46 (1H, s), 7.02 (1H, dd, J=7, 7Hz), 7.19 (1H, dd, J=7, 7Hz), 7.44 (1H, d, J=7Hz), 7.62 (1H, d, J=7Hz), 7.72 (1H, d, J=7Hz), 7.93 (1H, s)

MASS (m/z) : 328 (M⁺+1), 76 (bp)Example 52

The following compound was prepared in a similar manner to that of Example 32.

Methyl 1-(2-chlorobenzyl)-2-ethyl-3-formylindole-6-carboxylate

mp : 168-169°C

IR (KBr) : 1715, 1650 cm⁻¹

NMR (CDCl₃, δ) : 1.27 (3H, t, J=7Hz), 3.06 (2H, q, J=7Hz), 3.90 (3H, s), 5.50 (2H, s), 6.18 (1H, d,

- 133 -

J=7Hz), 7.05 (1H, t, J=7Hz), 7.21-7.24 (1H, m),
7.48 (1H, d, J=7.5Hz), 7.95 (1H, s), 8.01 (1H, d,
J=7Hz), 8.28 (1H, d, J=7Hz), 10.25 (1H, s)

MASS (m/z) : 356 (M⁺+1), 76 (bp)

5

Example 53

A mixture of 1-(2-chlorobenzyl)-3-isobutyryl-2-propylindole-6-carboxylic acid (100 mg), diphenylphosphoryl azide (97 mg) and triethylamine (53 mg) in tert-butanol (4 ml) was refluxed for 2 hours, and then partitioned between ethyl acetate and diluted with hydrochloric acid. The organic layer was washed with aqueous sodium bicarbonate and brine, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by silica gel thin layer chromatography with a mixture of hexane and ethyl acetate (2:1) to give 6-tert-butoxycarbonylamino-1-(2-chlorobenzyl)-3-isobutyryl-2-propylindole (125 mg) as a pale yellow oil.

NMR (CDCl₃, δ) : 0.98 (3H, t, J=7Hz), 1.28 (6H, d, J=7Hz), 1.48 (9H, s), 1.52-1.64 (2H, m), 2.96-3.02 (2H, m), 3.54 (1H, septet, J=7Hz), 5.42 (2H, s), 6.30 (1H, d, J=8Hz), 6.52 (1H, s), 7.05 (1H, t, J=8Hz), 7.09 (1H, d, J=8Hz), 7.20 (1H, t, J=8Hz), 7.36-7.45 (2H, m), 7.82 (1H, d, J=8Hz)

25 Example 54

To a solution of 6-tert-butoxycarbonylamino-1-(2-chlorobenzyl)-3-isobutyryl-2-propylindole (110 mg) in ethyl acetate (1 ml) was added 4N hydrogen chloride in ethyl acetate at 20°C, and the mixture was stirred at the same temperature for 4 hours. The precipitates were collected by filtration and washed with ethyl acetate to give 6-amino-1-(2-chlorobenzyl)-3-isobutyryl-2-propylindole hydrochloride (50 mg) as powder.

NMR (DMSO-d₆, δ) : 0.92 (3H, t, J=7Hz), 1.18 (6H, d, J=7Hz), 1.49 (2H, sextet, J=7Hz), 3.02-3.08 (2H,

35



- 134 -

m), 3.52 (1H, septet, $J=7\text{Hz}$), 5.58 (2H, s), 6.24 (1H, d, $J=8\text{Hz}$), 7.17-7.35 (4H, m), 7.57 (1H, d, $J=8\text{Hz}$), 8.02 (1H, d, $J=8\text{Hz}$)

5 Example 55

To a stirred solution of 6-tert-butoxycarbonylamino-1-(2-chlorobenzyl)-3-isobutyryl-2-propylindole (581 mg) in ethyl acetate (5 ml) was added 4N hydrogen chloride in ethyl acetate (5 ml) at 20°C. The reaction mixture was stirred at
10 20°C for 6.5 hours, then diluted with 1N aqueous sodium hydroxide and extracted. The organic phase was dried over magnesium sulfate and evaporated in vacuo. The residue was chromatographed on silica gel eluting with a mixture of ethyl acetate and hexane (1:6 to 1:4) to give 6-amino-1-(2-
15 chlorobenzyl)-3-isobutyryl-2-propylindole (361 mg) as yellow oil.

NMR (CDCl_3 , δ) : 1.00 (3H, t, $J=7\text{Hz}$), 1.29 (6H, d, $J=7\text{Hz}$), 1.51-1.64 (2H, m), 2.98-3.03 (2H, m), 3.49-3.57 (1H, m), 5.34 (2H, s), 6.36 (1H, d, $J=7.5\text{Hz}$),
20 6.46 (1H, s), 6.71 (1H, d, $J=7.5\text{Hz}$), 7.08 (1H, t, $J=7.5\text{Hz}$), 7.21 (1H, t, $J=7.5\text{Hz}$), 7.45 (1H, d, $J=7.5\text{Hz}$), 7.85 (1H, d, $J=7.5\text{Hz}$)

MASS (m/z) : 369 (M^++1)

25 Example 56

To a stirred solution of 6-amino-1-(2-chlorobenzyl)-3-isobutyryl-2-propylindole (79 mg) and triethylamine (0.065 ml) in dichloromethane (2 ml) was added acetyl chloride (0.02 ml) at 0°C. The reaction mixture was stirred at 20°C for 2
30 hours, then diluted with dichloromethane. The organic phase was washed with 1N hydrochloric acid, water, aqueous sodium bicarbonate, water and brine, dried over magnesium sulfate and evaporated in vacuo. The residue was chromatographed on silica gel eluting with a mixture of ethyl acetate and hexane
35 (2:3) to give crystals which were recrystallized from a

- 135 -

mixture of ethyl acetate and hexane to give 6-acetamide-1-(2-chlorobenzyl)-3-isobutyryl-2-propylindole (48 mg) as colorless crystals.

mp : 147-148°C

5 IR (KBr) : 1664, 1648, 1507, 1412 cm⁻¹

NMR (CDCl₃, δ) : 1.00 (3H, t, J=7Hz), 1.29 (6H, d, J=7Hz), 1.51-1.65 (2H, m), 2.17 (3H, s), 2.99-3.05 (2H, m), 3.49-3.58 (1H, m), 5.43 (2H, s), 6.30 (1H, d, J=7.5Hz), 7.04 (1H, t, J=7.5Hz), 7.13-7.23 (3H, m), 7.44 (1H, d, J=7.5Hz), 7.72 (1H, s), 7.85 (1H, d, J=7.5Hz)

10 MASS (m/z) : 411 (M⁺+1)

Example 57

15 To a stirred solution of 6-amino-1-(2-chlorobenzyl)-3-isobutyryl-2-propylindole (100 mg) in chloroform (2 ml) was added methylisocyanate (0.5 ml) at 0°C. The reaction mixture was stirred at 20°C for 1 hour, then evaporated. The residue was chromatographed on silica gel eluting with a mixture of
20 ethyl acetate and hexane (1:1) to give crystals which were recrystallized from a mixture of ethyl acetate and hexane to give 1-(2-chlorobenzyl)-3-isobutyryl-6-(3-methylureido)-2-propylindole (75 mg) as colorless crystals.

mp : 106-108.5°C

25 IR (KBr) : 1635, 1550, 1506 cm⁻¹

NMR (CDCl₃, δ) : 1.01 (3H, t, J=7Hz), 1.30 (6H, d, J=7Hz), 1.53-1.65 (2H, m), 2.78 (3H, d, J=7Hz), 3.00-3.06 (2H, m), 3.49-3.57 (1H, m), 4.61 (1H, d, J=7Hz), 5.42 (2H, s), 6.29-6.32 (2H, m), 7.02-7.07 (2H, m), 7.22 (1H, ddd, J=7.5, 7.5, 1Hz), 7.46 (1H, d, J=7.5Hz), 7.88 (1H, d, J=7.5Hz)

30 MASS (m/z) : 426 (M⁺+1), 76 (bp)

Example 58

35 To a stirred solution of 6-amino-1-(2-chlorobenzyl)-3-

- 136 -

isobutyryl-2-propylindole (147 mg) in dichloromethane (2 ml) was added acetic formic anhydride (0.5 ml) at 0°C. The reaction mixture was stirred at 0°C for 10 minutes, then diluted with dichloromethane. The organic phase was washed
5 with water and brine, dried over magnesium sulfate and evaporated in vacuo. The residue was chromatographed on silica gel eluting with a mixture of ethyl acetate and hexane (1:2) to give crystals which were recrystallized from a mixture of ethyl acetate and hexane to give 1-(2-
10 chlorobenzyl)-6-formamido-3-isobutyryl-2-propylindole (85 mg) as colorless crystals.

mp : 113-115°C

IR (KBr) : 1666, 1647, 1508 cm^{-1}

NMR (CDCl_3 , δ) : 1.00, 1.03 (3H, t and t, $J=7\text{Hz}$),
15 1.28, 1.30 (6H, d and d, $J=7\text{Hz}$), 1.54-1.65 (2H, m),
2.99-3.09 (2H, m), 3.47-3.57 (1H, m), 5.43 (2H, d, $J=4\text{Hz}$), 6.31 (1H, d, $J=7.5\text{Hz}$), 6.82-7.10 (2H, m),
7.17-7.25 (2H, m), 7.43-7.77 (2H, m), 7.90 (1H, dd, $J=10, 7.5\text{Hz}$), 8.37-8.58 (1H, m)

20 MASS (m/z) : 397 ($\text{M}^+ + 1$)

Example 59

A solution of 3-isobutyryl-1-(2-nitrobenzyl)-2-propylindole-6-carboxamide (316 mg) in methanol (10 ml) was
25 hydrogenated over 10% palladium on carbon at 20°C for 6 hours. The catalyst was filtered off and the filtrate was evaporated in vacuo. The residue was chromatographed on silica gel eluting with a mixture of methanol and chloroform (1:30) to give an oil which was dissolved in a mixture of
30 chloroform (10 ml) and methanol (20 ml). To this solution was added 10% hydrogen chloride in methanol (0.9 ml), and the mixture was stirred at 20°C for 1 hour and evaporated in vacuo. The residue was recrystallized from a mixture of methanol and diisopropyl ether to give 1-(2-aminobenzyl)-3-
35 isobutyryl-2-propylindole-6-carboxamide hydrochloride (415

- 137 -

mg) as colorless crystals.

mp : 255-257°C

IR (KBr) : 1650, 1550, 1455 cm^{-1}

5 NMR (DMSO- d_6 , δ) : 0.95 (3H, t, $J=7\text{Hz}$), 1.20 (3H, t, $J=7\text{Hz}$), 1.46-1.59 (2H, m), 2.96-3.01 (2H, m), 5.67 (2H, s), 5.89 (1H, d, $J=7.5\text{Hz}$), 6.87 (1H, br t, $J=7\text{Hz}$), 7.19-7.34 (3H, m), 7.80 (1H, d, $J=7.5\text{Hz}$), 7.92-7.98 (2H, m), 8.03 (1H, s)

10 MASS (m/z) : 378 (M^++1), 86 (bp)

Example 60

To a solution of 1-(2-chlorobenzyl)-3-methoxyacetyl-2-propylindole-6-carboxamide (168 mg) in a mixture of dichloromethane (10 ml) and methanol (0.5 ml) was added 1M solution of boron tribromide in dichloromethane (2.5 ml) at -53°C. The reaction mixture was warmed gradually to -12°C during 3 hours. Then 1M solution of boron tribromide in dichloromethane (2.5 ml) was added, and the mixture was stirred for 20 minutes at -12°C. The reaction mixture was diluted with water and extracted with 10% methanol in chloroform. The organic phase was washed with aqueous sodium bicarbonate, water and brine, dried over magnesium sulfate and evaporated in vacuo. The residue was crystallized from ethyl acetate and washed with hexane to give 1-(2-chlorobenzyl)-3-hydroxyacetyl-2-propylindole-6-carboxamide (120 mg) as colorless crystals.

mp : 231-233.5°C

IR (KBr) : 3405, 3159, 1673, 1647, 1616, 1395 cm^{-1}

30 NMR (DMSO- d_6 , δ) : 0.94 (3H, t, $J=7\text{Hz}$), 1.40-1.52 (2H, m), 3.05 (3H, t, $J=7\text{Hz}$), 4.75 (2H, t, $J=6\text{Hz}$), 4.90 (1H, t, $J=6\text{Hz}$), 5.65 (2H, s), 6.22 (1H, d, $J=7.5\text{Hz}$), 7.18 (1H, t, $J=7.5\text{Hz}$), 7.27-7.35 (2H, m), 7.58 (1H, d, $J=7.5\text{Hz}$), 7.81 (1H, d, $J=7.5\text{Hz}$), 7.92 (2H, d, $J=7.5\text{Hz}$), 8.01 (1H, s)

35 MASS (m/z) : 385 (M^++1), 86 (bp)



- 138 -

Example 61

To a stirred mixture of benzyl 3-isobutyryl-2-propylindole-6-carboxylate (207 mg) and diisopropylethylamine (295 mg) in dichloromethane (6 ml) were added 2-chlorobenzoyl chloride (299 mg) and 4-dimethylaminopyridine (12 mg) at 0°C. The reaction mixture was refluxed for 15 hours. The reaction mixture was cooled to 20°C and washed with 1N hydrochloric acid, water, saturated sodium bicarbonate, water and brine. The organic phase was dried over sodium sulfate and evaporated in vacuo. The residue was chromatographed on silica gel eluting with a mixture of ethyl acetate and hexane (1:10) to give benzyl 1-(2-chlorobenzoyl)-3-isobutyryl-2-propylindole-6-carboxylate (330 mg) as yellow crystals.

mp : 67.5-70°C

IR (KBr) : 1780, 1710, 1700, 1300 cm^{-1}

NMR (CDCl_3 , δ) : 0.99 (3H, t, $J=7\text{Hz}$), 1.27 (6H, t, $J=7\text{Hz}$), 1.74 (2H, sextet, $J=7\text{Hz}$), 3.12 (2H, t, $J=7\text{Hz}$), 3.39-3.48 (1H, m), 5.25 (2H, s), 7.33-7.45 (8H, m), 7.53-7.58 (2H, m), 7.80 (1H, d, $J=7.5\text{Hz}$), 7.98-8.05 (1H, m)

MASS (m/z) : 502 ($M^+ + 1$)Example 62

A solution of benzyl 1-(2-chlorobenzoyl)-3-isobutyryl-2-propylindole-6-carboxylate (304 mg) in methanol (6 ml) was hydrogenated over 10% palladium on carbon at 20°C for 9 hours. The catalyst was filtered off and the filtrate was evaporated in vacuo. The residue was chromatographed on silica gel eluting with a mixture of methanol and chloroform (1:30) to give crystals which were recrystallized from a mixture of ethyl acetate and hexane to give 1-(2-chlorobenzoyl)-3-isobutyryl-2-propylindole-6-carboxylic acid (189 mg) as colorless crystals.

IR (KBr) : 1710, 1695, 1980, 1315 cm^{-1} NMR (CDCl_3 , δ) : 0.95 (3H, t, $J=7\text{Hz}$), 1.27 (6H, t,

- 139 -

J=7Hz), 1.64-1.75 (2H, m), 3.03-3.09 (1H, m), 3.40-3.49 (1H, m), 7.48-7.52 (2H, m), 7.58-7.67 (3H, m), 7.92 (2H, AB, J=8, 7.5Hz)

5 Example 63

To a stirred solution of 1-(2-chlorobenzyl)-3-formylindole-6-carboxamide (47 mg) in dimethylformamide (1.6 ml) was added chromic anhydride (125 mg) and sulfuric acid (0.05 ml), and the mixture was stirred at 20°C for 5
10 hours. The resulting mixture was evaporated in vacuo and the residue was chromatographed on silica gel eluting with a mixture of chloroform and methanol (9:1) to give 6-carbamoyl-1-(2-chlorobenzyl)indole-3-carboxylic acid (8.3 mg) as a solid.

15 mp : 240°C (dec.)

NMR (DMSO-d₆, δ) : 5.64 (2H, s), 6.71 (1H, d, J=8Hz),
7.26 (1H, t, J=8Hz), 7.28 (1H, br s), 7.36 (1H, t, J=8Hz), 7.56 (1H, d, J=8Hz), 7.78 (1H, d, J=8Hz),
7.92 (1H, br s), 8.06 (1H, s), 8.07 (1H, d, J=8Hz),
20 8.20 (1H, s)

Example 64

To a solution of 1-(2-chlorobenzyl)-2-(1-hydroxypropyl)-3-isobutyrylindole-6-carboxamide (19 mg) in acetone (3 ml)
25 was added Jones's reagent until the red color existed continuously. The reaction was quenched by 2-propanol, then the mixture was diluted with ethyl acetate and washed with aqueous sodium bicarbonate and brine. The organic phase was dried over sodium sulfate and evaporated in vacuo. The
30 residue was triturated with diisopropyl ether to give 1-(2-chlorobenzyl)-3-isobutyryl-2-propionylindole-6-carboxamide (9.3 mg).

mp : 145-147°C

NMR (CDCl₃, δ) : 1.15 (3H, t, J=7Hz), 1.33 (6H, d, J=7Hz), 2.60 (2H, q, J=7Hz), 3.47 (1H, m), 5.46
35

- 140 -

(2H, s), 6.50 (1H, d, J=8Hz), 7.09 (1H, t, J=8Hz),
7.21 (1H, t, J=8Hz), 7.42 (1H, d, J=8Hz), 7.70 (1H,
d, J=8Hz), 7.88 (1H, s), 7.98 (1H, s)

5 Example 65

The following compound was prepared in a similar manner
to that of Preparation 45.

3-Chloro-1-(2-chlorobenzyl)-2-propylindole-6-carboxamide
10 mp : 163-166°C
NMR (CDCl₃, δ) : 0.95 (3H, t, J=7Hz), 1.58 (2H, m),
2.73 (2H, t, J=7Hz), 5.43 (2H, s), 6.19 (1H, d,
J=8Hz), 7.01 (1H, t, J=8Hz), 7.18 (1H, t, J=8Hz),
7.43 (1H, d, J=8Hz), 7.54 (1H, d, J=8Hz), 7.67 (1H,
15 d, J=8Hz), 7.82 (1H, s)

Example 66

To a stirred solution of methyl 1-(2-bromobenzyl)-2-
propylindole-6-carboxamide (52 mg) in a mixture of
20 dichloromethane (3 ml) and pyridine (1 ml) was added
pyridinium bromide perbromide (50 mg), and the mixture was
stirred at 0°C for 1.5 hours. The resulting mixture was
diluted with ethyl acetate and washed with diluted
hydrochloric acid, aqueous sodium bicarbonate and brine, then
25 dried over sodium sulfate and evaporated in vacuo. The
residue was triturated with a mixture of hexane and
diisopropyl ether to give 3-bromo-1-(2-bromobenzyl)-2-
propylindole-6-carboxamide (33 mg) as a solid.

mp : 122-125°C
30 NMR (CDCl₃, δ) : 0.98 (3H, t, J=7Hz), 1.57 (2H, m),
2.73 (2H, t, J=7Hz), 5.42 (2H, s), 6.15 (1H, d,
J=8Hz), 7.0-7.16 (2H, m), 7.5-7.65 (3H, m), 7.79
(1H, s)

35 Example 67

- 141 -

The following compounds described in (1) to (2) were prepared in a similar manner to that of Example 42.

(1) 1-(2-Chlorobenzyl)-3-isobutyryl-2-propylindole-6-carbonitrile

mp : 130-131°C

NMR (CDCl₃, δ) : 1.03 (3H, t, J=7Hz), 1.30 (6H, d, J=7Hz), 1.56-1.68 (2H, m), 3.06-3.12 (2H, m), 3.51 (1H, septet, J=7Hz), 5.46 (2H, s), 6.23 (1H, d, J=8Hz), 7.08 (1H, t, J=8Hz), 7.27 (1H, t, J=8Hz), 7.46-7.52 (3H, m), 8.01 (1H, d, J=8Hz)

(2) 9-(2-Chlorobenzyl)-8-oxo-5,6,7,8-tetrahydrocarbazole-2-carbonitrile

mp : 173-176°C

NMR (CDCl₃, δ) : 2.29 (2H, m), 2.69 (2H, t, J=7Hz), 3.08 (2H, t, J=7Hz), 5.94 (2H, s), 6.30 (1H, d, J=8Hz), 7.02 (1H, t, J=8Hz), 7.19 (1H, t, J=8Hz), 7.38 (1H, d, J=8Hz), 7.42 (1H, d, J=8Hz), 7.54 (1H, s), 7.78 (1H, d, J=8Hz)

Example 68

To a solution of 1-(2-chlorobenzyl)-3-isobutyryl-2-propylindole-6-carbonitrile (70 mg) in a mixture of methanol (2 ml) and tetrahydrofuran (2 ml) was added sodium borohydride (21 mg) at 25°C. After stirred at 25°C for 2 hours, the reaction mixture was partitioned between ethyl acetate and 1N hydrochloric acid. The organic layer was washed with water and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was crystallized from diisopropyl ether to give 1-(2-chlorobenzyl)-3-(1-hydroxy-2-methylpropyl)-2-propylindole-6-carbonitrile (28 mg) as pale yellow crystals.

mp : 126-127°C

NMR (CDCl₃, δ) : 0.76 (3H, d, J=7Hz), 0.98 (3H, t,

- 142 -

J=7Hz), 1.22 (3H, d, J=7Hz), 1.50-1.64 (2H, m),
1.87 (1H, d, J=2Hz), 2.32-2.44 (2H, m), 2.63-2.80
(2H, m), 4.58 (1H, dd, J=2, 8Hz), 5.38 (2H, s),
6.15 (1H, d, J=8Hz), 7.05 (1H, t, J=8Hz), 7.22 (1H,
5 t, J=8Hz), 7.32 (1H, d, J=8Hz), 7.38 (1H, s), 7.46
(1H, d, J=8Hz), 7.91 (1H, d, J=8Hz)

Example 69

The following compound was prepared in a similar manner
10 to that of Example 68.

1-(2-Chlorobenzyl)-2-ethyl-3-(1-hydroxy-2-methylpropyl)-
indole-6-carboxamide

mp : 169-172°C

15 NMR (CDCl₃, δ) : 0.78 (3H, d, J=7Hz), 1.17 (3H, t,
J=7Hz), 1.23 (3H, d, J=7Hz), 2.41 (1H, m), 2.74
(2H, m), 4.60 (1H, m), 5.43 (2H, s), 6.14 (1H, d,
J=8Hz), 6.98 (1H, t, J=8Hz), 7.17 (1H, t, J=8Hz),
7.4-7.5 (2H, m), 7.76 (1H, s), 7.85 (1H, d, J=8Hz)

20

Example 70

To a suspension of 3-acetyl-1-(2-chlorobenzyl)-2-
propylindole-6-carboxamide (36.5 mg) in ethanol (5 ml) was
added hydroxylamine hydrochloride (70 mg) and sodium acetate
25 (200 mg), and the mixture was heated in a sealed tube at
100°C. The reaction was evaporated in vacuo, then the
residue was diluted with ethyl acetate and washed with water
and brine. The organic phase was dried over sodium sulfate
and evaporated in vacuo. The residue was triturated with
30 diisopropyl ether to give 1-(2-chlorobenzyl)-3-(1-
hydroxyiminoethyl)-2-propylindole-6-carboxamide (32.7 mg).

mp : 212-216°C

35 NMR (CDCl₃, δ) : 0.94 (3H, t, J=7Hz), 1.56 (2H, m),
2.39 (3H, s), 2.80 (2H, m), 5.45 (2H, s), 6.21 (1H,
d, J=8Hz), 6.99 (1H, t, J=8Hz), 7.20 (1H, t,

- 143 -

J=8Hz), 7.42 (1H, d, J=8Hz), 7.50 (1H, m), 7.70-7.78 (2H, m)

Example 71

5 1-(2-Aminobenzyl)-3-isobutyryl-2-propylindole-6-carboxamide hydrochloride (111 mg) was dissolved in chloroform, and the solution was washed with 1N aqueous sodium hydroxide, dried over magnesium sulfate and evaporated in vacuo. The residue was dissolved in chloroform (3 ml),
10 and then methyl isocyanate (1.5 ml) was added at 0°C. After stirred at 20°C for 2 hours, the mixture was evaporated in vacuo. The residue was dissolved in a mixture of ethyl acetate and tetrahydrofuran, and the solution was washed with water and brine, dried over magnesium sulfate and evaporated
15 in vacuo. The crystalline residue was recrystallized from a mixture of 1,4-dioxane and hexane to give 3-isobutyryl-1-[2-(3-methylureido)benzyl]-2-propylindole-6-carboxamide (74 mg) as colorless crystals.

mp : 222-223°C

20 IR (KBr) : 1648, 1617, 1557 cm⁻¹

NMR (DMSO-d₆, δ) : 0.91 (3H, t, J=7Hz), 1.18 (6H, d, J=7Hz), 1.42-1.50 (2H, m), 2.71 (3H, d, J=5Hz), 2.92-3.00 (2H, m), 3.50-3.56 (1H, m), 5.48 (2H, s), 5.99 (1H, d, J=8Hz), 6.34-6.39 (1H, m), 6.86 (1H, t, J=7.5Hz), 7.18 (1H, t, J=7.5Hz), 7.28 (1H, s),
25 7.55 (1H, t, J=7.5Hz), 7.78 (1H, d, J=7.5Hz), 7.92-7.97 (3H, m), 8.21 (1H, s)

MASS (m/z) : 435 (M⁺+1), 86 (bp)

30 Example 72

To a solution of methyl 1-(2-chlorobenzyl)-2-propylindole-6-carboxylate (200 mg) in trifluoroacetic acid (2 ml) was added concentrated nitric acid (0.3 ml) at 0°C. After stirred at 0°C for 30 minutes, the reaction mixture was
35 partitioned between ethyl acetate and water. The organic

- 144 -

layer was washed with aqueous sodium bicarbonate, water and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by preparative thin layer chromatography on silica gel eluting with a mixture of ethyl acetate and hexane (1:3) to give methyl 1-(2-chlorobenzyl)-3-nitro-2-propylindole-6-carboxylate (73 mg) as pale yellow crystals.

5 NMR (CDCl₃, δ) : 1.04 (3H, t, J=7Hz), 1.68 (2H, sextet, J=7Hz), 3.14-3.18 (2H, m), 3.91 (3H, s),
10 5.13 (2H, s), 6.32 (1H, d, J=8Hz), 7.08 (1H, t, J=8Hz), 7.27 (1H, t, J=8Hz), 7.48 (1H, d, J=8Hz),
7.98 (1H, s), 8.08 (1H, d, J=8Hz), 8.43 (1H, d, J=8Hz)

15 Example 73

The following compounds described in (1) to (44) were prepared in a similar manner to that of Example 1.

(1) Methyl 1-(2-chlorobenzyl)-2-(3-methoxycarbonylpropyl)-
20 indole-6-carboxylate

NMR (CDCl₃, δ) : 2.04 (2H, m), 2.88 (2H, t, J=7Hz),
2.69 (2H, t, J=7Hz), 3.62 (3H, s), 3.89 (3H, s),
5.43 (2H, s), 6.14 (1H, d, J=8Hz), 6.46 (1H, s),
7.01 (1H, t, J=8Hz), 7.18 (1H, t, J=8Hz), 7.42 (1H,
25 d, J=8Hz), 7.59 (1H, d, J=8Hz), 7.80 (1H, d,
J=8Hz), 7.90 (1H, s)

(2) Methyl 1-(2-chlorobenzyl)-2-(2-methoxycarbonylethyl)-
indole-6-carboxylate

30 NMR (CDCl₃, δ) : 2.77 (2H, m), 2.98 (2H, m), 3.69 (3H, s),
3.88 (3H, s), 5.45 (2H, s), 6.16 (1H, d, J=8Hz),
6.41 (1H, s), 7.02 (1H, t, J=8Hz), 7.19 (1H, t, J=8Hz),
7.42 (1H, d, J=8Hz), 7.60 (1H, d, J=8Hz), 7.81 (1H, d, J=8Hz),
7.91 (1H, s)

35

- 145 -

(3) Methyl 1-(2-chlorobenzyl)-3-isobutyryl-2-propylindole-7-carboxylate

5 NMR (CDCl₃, δ) : 1.02 (3H, t, J=7Hz), 1.79 (6H, d, J=7Hz), 1.63 (2H, m), 3.01 (2H, m), 3.52 (1H, m), 3.56 (3H, s), 5.61 (2H, s), 6.08 (1H, d, J=8Hz), 6.98 (1H, t, J=8Hz), 7.17 (1H, t, J=8Hz), 7.2-7.45 (3H, m), 8.12 (1H, d, J=8Hz)

10 (4) Methyl 1-(2-chlorobenzyl)-3-isobutyryl-2-propylindole-5-carboxylate

15 NMR (CDCl₃, δ) : 1.03 (3H, t, J=8Hz), 1.34 (6H, d, J=8Hz), 1.62 (2H, sextet, J=8Hz), 3.06-3.10 (2H, m), 3.64 (1H, septet, J=8Hz), 3.96 (3H, s), 5.47 (2H, s), 6.26 (1H, d, J=8Hz), 7.06 (1H, t, J=8Hz), 7.20 (1H, t, J=8Hz), 7.25 (1H, d, J=8Hz), 7.47 (1H, dd, J=1, 8Hz), 7.92 (1H, d, J=8Hz), 8.68 (1H, d, J=1Hz)

20 (5) Methyl 1-(6-chloro-3,4-methylenedioxybenzyl)-3-isobutyryl-2-propylindole-5-carboxylate

25 NMR (CDCl₃, δ) : 1.05 (3H, t, J=8Hz), 1.32 (6H, d, J=8Hz), 1.62 (2H, sextet, J=8Hz), 3.06 (2H, t, J=8Hz), 3.63 (1H, septet, J=8Hz), 3.96 (3H, s), 5.36 (2H, s), 5.74 (1H, s), 5.88 (2H, s), 6.92 (1H, s), 7.20 (1H, d, J=10Hz), 7.82 (1H, d, J=10Hz), 8.76 (1H, s)

(6) Methyl 1-(2-chlorobenzyl)-2-propylindole-4-carboxylate

30 NMR (CDCl₃, δ) : 1.01 (3H, t, J=7Hz), 1.78 (2H, m), 2.67 (2H, t, J=7Hz), 3.99 (3H, s), 5.42 (2H, s), 6.18 (1H, d, J=8Hz), 7.01 (1H, t, J=8Hz), 7.03 (1H, s), 7.11 (1H, t, J=8Hz), 7.18 (1H, t, J=8Hz), 7.30 (1H, d, J=8Hz), 7.43 (1H, d, J=8Hz), 7.89 (1H, d, J=8Hz)

35

- 146 -

(7) Methyl 9-(2-chlorobenzyl)-8-oxo-5,6,7,8-tetrahydrocarbazole-2-carboxylate

5 NMR (CDCl₃, δ) : 2.27 (2H, m), 2.67 (2H, t, J=7Hz),
3.11 (2H, t, J=7Hz), 3.90 (3H, s), 5.95 (2H, s),
6.25 (1H, d, J=8Hz), 6.98 (1H, t, J=8Hz), 7.15 (1H,
t, J=8Hz), 7.40 (1H, d, J=8Hz), 7.74 (1H, d,
J=8Hz), 7.84 (1H, d, J=8Hz), 7.99 (1H, s)

10 (8) Methyl 9-(6-chloro-3,4-methylenedioxybenzyl)-8-oxo-5,6,7,8-tetrahydrocarbazole-2-carboxylate

NMR (CDCl₃, δ) : 2.18 (2H, m), 2.63 (2H, t, J=7Hz),
3.07 (2H, t, J=7Hz), 3.84 (3H, s), 5.68 (1H, s),
5.83 (2H, s), 5.96 (2H, s), 7.18 (1H, s), 7.84 (1H,
d, J=8Hz), 7.92 (1H, d, J=8Hz), 8.03 (1H, s)

15

(9) Methyl 1-(4-bromo-2-chlorobenzyl)-3-isobutyryl-2-propylindole-6-carboxylate

mp : 65-67°C

IR (KBr) : 1715, 1705, 1656, 1456, 1433 cm⁻¹

20 NMR (CDCl₃, δ) : 1.03 (3H, t, J=7Hz), 1.30 (6H, d,
J=7Hz), 1.52-1.64 (2H, m), 2.99-3.05 (2H, m), 3.51-
3.60 (1H, m), 3.92 (3H, s), 5.45 (2H, s), 6.09 (1H,
d, J=7.5Hz), 7.18 (1H, d, J=7.5Hz), 7.66 (1H, s),
7.90 (1H, s), 7.99 (2H, s)

25

MASS (m/z) : 492 (M⁺+2)

(10) 1-(2-Acetamidobenzyl)-3-isobutyryl-2-propylindole-6-carboxamide

mp : 235-236°C

30 IR (KBr) : 1693, 1656, 1457 cm⁻¹

NMR (CDCl₃, δ) : 0.91 (3H, t, J=7Hz), 1.18 (6H, d,
J=7Hz), 1.39-1.50 (2H, m), 2.17 (3H, s), 2.92-2.99
(2H, m), 3.50-3.59 (1H, m), 5.49 (2H, s), 6.07 (1H,
d, J=7.5Hz), 7.00 (1H, t, J=7.5Hz), 7.21-7.29 (2H,
35 m), 7.39 (1H, d, J=7.5Hz), 7.79 (1H, d, J=7.5Hz),

- 147 -

7.92-7.96 (3H, m), 9.85 (1H, s)

MASS (m/z) : 420 ($M^+ + 1$), 86 (bp)

(11) Methyl 1-(2-chlorobenzyl)-3-formylindole-6-carboxylate

5 NMR ($CDCl_3$, δ) : 3.93 (3H, s), 5.52 (2H, s), 6.88 (1H, dd, $J=1$, 8Hz), 7.21 (1H, dt, $J=1$, 8Hz), 7.32 (1H, dt, $J=1$, 8Hz), 7.49 (1H, dd, $J=1$, 8Hz), 7.82 (1H, s), 8.02 (1H, dd, $J=1$, 8Hz), 8.13 (1H, d, $J=1$ Hz), 8.36 (1H, d, $J=8$ Hz), 10.0 (1H, s)

10

(12) Methyl 3-acetyl-1-(2-chlorobenzyl)-2-methylindole-6-carboxylate

This compound was used immediately without purification.

15

(13) Methyl 1-(2-chlorobenzyl)-2-methyl-3-propionylindole-6-carboxylate

20 NMR ($CDCl_3$, δ) : 1.31 (3H, t, $J=7$ Hz), 2.70 (3H, s), 3.09 (2H, q, $J=7$ Hz), 3.90 (3H, s), 5.50 (2H, s), 6.22 (1H, d, $J=8$ Hz), 7.04 (1H, t, $J=8$ Hz), 7.24 (1H, t, $J=8$ Hz), 7.46 (1H, d, $J=8$ Hz), 7.92-7.98 (2H, m), 8.08 (1H, d, $J=8$ Hz)

25 (14) Methyl 1-(2-chlorobenzo[b]thiophen-3-ylmethyl)-3-isobutyryl-2-methylindole-6-carboxylate

NMR ($DMSO-d_6$, δ) : 1.14 (6H, d, $J=7$ Hz), 2.72 (3H, s), 3.48 (1H, m), 3.81 (3H, s), 5.91 (2H, s), 7.3-7.5 (3H, m), 7.80 (1H, d, $J=8$ Hz), 7.98 (1H, d, $J=8$ Hz), 8.06 (1H, d, $J=8$ Hz), 8.19 (1H, s)

30

(15) Methyl 1-(benzothiazol-2-ylmethyl)-2-ethyl-3-isobutyrylindole-6-carboxylate

35 NMR ($CDCl_3$, δ) : 1.28 (3H, t, $J=7$ Hz), 1.30 (6H, d, $J=7$ Hz), 3.24 (2H, q, $J=7$ Hz), 3.53 (1H, m), 3.91 (3H, s), 5.82 (2H, s), 7.25-7.53 (2H, m), 7.72 (1H,

- 148 -

m), 7.8-8.1 (3H, m), 8.18 (1H, s)

(16) Methyl 1-(benzo[b]thiophen-5-ylmethyl)-3-isobutyryl-2-propylindole-6-carboxylate

5 NMR (CDCl₃, δ) : 1.02 (3H, t, J=7Hz), 1.32 (6H, d, J=7Hz), 1.62 (2H, m), 3.13 (2H, m), 3.57 (1H, m), 3.87 (3H, s), 5.57 (2H, s), 7.03 (1H, d, J=8Hz), 7.18 (1H, d, J=6Hz), 7.29 (1H, s), 7.44 (1H, d, J=6Hz), 7.79 (1H, d, J=8Hz), 7.94 (2H, s), 8.02
10 (1H, s)

(17) Methyl 1-allyl-3-isobutyryl-2-propylindole-6-carboxylate

15 NMR (CDCl₃, δ) : 1.07 (3H, t, J=7Hz), 1.28 (6H, d, J=7Hz), 1.69 (2H, m), 3.12 (2H, m), 3.54 (1H, m), 3.94 (3H, s), 4.84 (2H, m), 4.87 (1H, m), 5.22 (1H, m), 5.98 (1H, m), 7.89 (1H, d, J=8Hz), 7.94 (1H, d, J=8Hz), 8.04 (1H, s)

(18) Methyl 1-(2-chlorobenzyl)-3-isobutyryl-2-(1-propenyl)indole-6-carboxylate

20 NMR (CDCl₃, δ) : 1.23 (6H, d, J=7Hz), 1.93 (3H, d, J=7Hz), 3.51 (1H, m), 3.89 (3H, s), 5.50 (2H, s), 6.41 (1H, m), 6.42 (1H, d, J=8Hz), 6.73 (1H, d, J=16Hz), 7.07 (1H, t, J=8Hz), 7.23 (1H, t, J=8Hz), 7.47 (1H, d, J=8Hz), 7.89 (1H, s), 7.95 (1H, d, J=8Hz), 8.18 (1H, d, J=8Hz)
25

(19) Methyl 2-(1-acetoxypentyl)-1-(2-chlorobenzyl)-3-isobutyrylindole-6-carboxylate

30 NMR (CDCl₃, δ) : 1.04 (3H, t, J=7Hz), 1.2-1.35 (9H, m), 1.9-2.1 (2H, m), 3.59 (1H, m), 3.89 (3H, s), 5.61 (1H, d, J=17Hz), 5.79 (1H, d, J=17Hz), 6.04 (1H, d, J=8Hz), 6.71 (1H, m), 7.01 (1H, t, J=8Hz), 7.21 (1H, t, J=8Hz), 7.47 (1H, d, J=8Hz), 7.87 (1H, s), 7.92 (1H, d, J=8Hz), 7.97 (1H, d, J=8Hz)
35

- 149 -

(20) Methyl 3-(3,3-dimethylbutanoyl)-1-(2-chlorobenzyl)indole-6-carboxylate

5 NMR (CDCl₃, δ) : 1.09 (9H, s), 2.69 (2H, s), 3.93 (3H, s), 5.50 (2H, s), 6.73 (1H, d, J=8Hz), 7.17 (1H, t, J=8Hz), 7.28 (1H, t, J=8Hz), 7.47 (1H, d, J=8Hz), 7.82 (1H, s), 8.00 (1H, d, J=8Hz), 8.08 (1H, s), 8.53 (1H, d, J=8Hz)

10 (21) Ethyl 1-(2-chlorobenzyl)-3-isobutyryl-2-propylindol-6-ylacetate

IR (Neat) : 1730, 1655 cm⁻¹

15 NMR (CDCl₃, δ) : 1.00 (3H, t, J=7Hz), 1.20 (3H, t, J=7Hz), 1.29 (6H, d, J=7Hz), 1.55-1.65 (2H, m), 3.01-3.08 (2H, m), 3.54-3.60 (1H, m), 3.69 (2H, s), 4.11 (2H, q, J=7Hz), 5.44 (2H, s), 6.30 (1H, d, J=7.5Hz), 7.03-7.10 (2H, m), 7.21 (2H, d, J=7.5Hz), 7.46 (1H, d, J=7.5Hz), 7.89 (1H, d, J=7.5Hz)

MASS (m/z) : 440 (M⁺+1), 74 (bp)

20 (22) Methyl 1-(6-chloro-3,4-methylenedioxybenzyl)-3-isobutyryl-2-propylindol-6-ylacetate

mp : 119-120.5°C

IR (KBr) : 1744, 1735, 1732, 1644, 1508 cm⁻¹

25 NMR (CDCl₃, δ) : 1.03 (3H, t, J=7Hz), 1.29 (6H, d, J=7Hz), 1.55-1.65 (2H, m), 3.00-3.07 (2H, m), 3.53-3.61 (1H, m), 3.70 (3H, s), 3.72 (2H, s), 5.33 (2H, s), 5.80 (2H, s), 5.91 (2H, s), 6.93 (1H, s), 7.01 (1H, s), 7.21 (1H, d, J=7.5Hz), 7.89 (1H, d, J=7.5Hz)

30 MASS (m/z) : 470 (M⁺+1), 74 (bp)

(23) Methyl 1-(2-chlorobenzyl)-2-propylindole-6-carboxylate

35 NMR (CDCl₃, δ) : 1.02 (3H, t, J=7Hz), 1.75 (2H, m), 2.62 (2H, t, J=7Hz), 3.87 (3H, s), 5.42 (2H, s), 6.16 (1H, d, J=8Hz), 6.42 (1H, s), 7.01 (1H, t,

- 150 -

J=8Hz), 7.19 (1H, t, J=8Hz), 7.42 (1H, t, J=8Hz),
7.58 (1H, t, J=8Hz), 7.79 (1H, d, J=8Hz), 8.92 (1H,
s)

5 (24) Methyl 1-(2-bromobenzyl)-2-propylindole-6-carboxylate

NMR (CDCl₃, δ) : 0.99 (3H, t, J=7Hz), 1.74 (2H, m),
2.59 (2H, t, J=7Hz), 3.88 (3H, s), 5.37 (2H, s),
6.12 (1H, d, J=8Hz), 6.42 (1H, s), 7.0-7.15 (2H,
m), 7.52-7.65 (2H, m), 7.79 (1H, d, J=8Hz),
10 7.89 (1H, s)

(25) Methyl 2-acetyl-1-(2-chlorobenzyl)-3-methylindole-6-
carboxylate

NMR (CDCl₃, δ) : 2.61 (3H, s), 2.71 (3H, s), 3.90 (3H,
15 s), 5.82 (2H, s), 6.19 (1H, d, J=8Hz), 6.97 (1H, t,
J=8Hz), 7.14 (1H, t, J=8Hz), 7.41 (1H, d, J=8Hz),
7.79 (1H, d, J=8Hz), 7.86 (1H, d, J=8Hz), 7.99 (1H,
s)

20 (26) Methyl 2-chloro-1-(2-chlorobenzyl)-3-ethylindole-6-
carboxylate

NMR (CDCl₃, δ) : 1.29 (3H, t, J=7Hz), 2.83 (2H, q,
J=7Hz), 3.90 (3H, s), 5.50 (2H, s), 6.29 (1H, d,
J=8Hz), 7.04 (1H, t, J=8Hz), 7.19 (1H, t, J=8Hz),
25 7.42 (1H, d, J=8Hz), 7.61 (1H, d, J=8Hz), 7.83 (1H,
d, J=8Hz), 7.90 (1H, s)

(27) Methyl 1-(2-chlorobenzyl)-2-propionyl-3-propylindole-6-
carboxylate

NMR (CDCl₃, δ) : 1.07 (3H, t, J=7Hz), 1.17 (3H, t,
30 J=7Hz), 1.78 (2H, m), 2.94 (2H, q, J=7Hz), 3.09
(2H, m), 3.89 (3H, s), 5.72 (2H, s), 6.23 (1H, d,
J=8Hz), 6.98 (1H, t, J=8Hz), 7.15 (1H, t, J=8Hz),
7.39 (1H, d, J=8Hz), 7.76 (1H, d, J=8Hz), 7.83 (1H,
35 d, J=8Hz), 7.96 (1H, s)

- 151 -

(28) Methyl 1-(2-chlorobenzyl)-2-isobutyryl-3-propylindole-6-carboxylate

5 NMR (CDCl₃, δ) : 1.03 (3H, t, J=7Hz), 1.11 (6H, d, J=7Hz), 1.75 (2H, m), 3.02 (2H, m), 3.35 (1H, m), 3.89 (3H, s), 5.64 (2H, s), 6.28 (1H, d, J=8Hz), 6.99 (1H, t, J=8Hz), 7.16 (1H, t, J=8Hz), 7.38 (1H, d, J=8Hz), 7.73 (1H, d, J=8Hz), 7.84 (1H, d, J=8Hz), 7.96 (1H, s)

10 (29) Methyl 1-(2-chlorobenzyl)-3-(3-oxo-1-butenyl)indole-6-carboxylate

15 NMR (CDCl₃, δ) : 2.38 (3H, s), 3.93 (3H, s), 5.48 (2H, s), 6.7-6.8 (2H, m), 7.17 (1H, t, J=8Hz), 7.28 (1H, t, J=8Hz), 7.47 (1H, d, J=8Hz), 7.54 (1H, s), 7.74 (1H, d, J=15Hz), 7.96 (1H, s), 8.11 (1H, s)

(30) Methyl 4-(2-chlorobenzyl)-3-oxo-1,2,3,4-tetrahydrocyclopent[b]indole-6-carboxylate

20 NMR (CDCl₃, δ) : 3.06 (2H, m), 3.17 (2H, m), 3.92 (3H, s), 5.72 (2H, s), 6.59 (1H, d, J=8Hz), 7.06 (1H, t, J=8Hz), 7.19 (1H, t, J=8Hz), 7.42 (1H, d, J=8Hz), 7.78 (1H, d, J=8Hz), 7.87 (1H, d, J=8Hz), 8.04 (1H, s)

25 (31) Methyl 4-(6-chloro-3,4-methylenedioxybenzyl)-3-oxo-1,2,3,4-tetrahydrocyclopent[b]indole-6-carboxylate

30 NMR (CDCl₃, δ) : 3.06 (3H, m), 3.14 (2H, m), 3.94 (3H, s), 5.60 (2H, s), 5.88 (2H, s), 6.11 (1H, s), 6.88 (1H, s), 7.76 (1H, d, J=8Hz), 7.86 (1H, d, J=8Hz), 8.09 (1H, s)

(32) 1-(2-Chlorobenzyl)-3-cyclopropanecarbonyl-2-propylindole-6-carboxamide

35 mp : 162-163.5°C
IR (KBr) : 1675, 1612, 1444, 1383 cm⁻¹

- 152 -

NMR (DMSO- d_6 , δ) : 0.90 (3H, t, J=7Hz), 1.08 (4H, d, J=7Hz), 1.48 (2H, sextet, J=7Hz), 2.65-2.72 (1H, m), 3.00 (2H, t, J=7Hz), 5.62 (2H, s), 6.21 (1H, d, J=8Hz), 7.18 (1H, t, J=8Hz), 7.32 (1H, t, J=8Hz), 7.58 (1H, d, J=8Hz), 7.80 (1H, d, J=8Hz), 7.93 (1H, s), 8.01 (1H, s), 8.10 (1H, d, J=7Hz)
MASS (m/z) : 395 (M^+ +1), 74 (bp)

(33) 1-(6-Chloro-3,4-methylenedioxybenzyl)-3-cyclopropanecarbonyl-2-propylindole-6-carboxamide
mp : 162-163.5°C
IR (KBr) : 1675, 1612, 1444, 1383 cm^{-1}
NMR (DMSO- d_6 , δ) : 0.90 (3H, t, J=7Hz), 1.08 (4H, d, J=7Hz), 1.48 (2H, sextet, J=7Hz), 2.65-2.72 (1H, m), 3.00 (2H, t, J=7Hz), 5.62 (2H, s), 6.21 (1H, d, J=8Hz), 7.18 (1H, t, J=8Hz), 7.32 (1H, t, J=8Hz), 7.58 (1H, d, J=8Hz), 7.80 (1H, d, J=8Hz), 7.93 (1H, s), 8.01 (1H, s), 8.10 (1H, d, J=7Hz)
MASS (m/z) : 395 (M^+ +1), 74 (bp)

(34) 1-(2-Chlorobenzyl)-3-cyclobutanecarbonyl-2-propylindole-6-carboxamide
mp : 162-165°C
IR (KBr) : 1660, 1654, 1445, 1437 cm^{-1}
NMR (CDCl_3 , δ) : 1.02 (3H, t, J=7Hz), 1.62 (2H, sextet, J=7Hz), 1.95-2.14 (2H, m), 2.35-2.52 (4H, m), 3.05-3.10 (2H, m), 4.05 (1H, quintet, J=7Hz), 5.50 (2H, s), 6.22 (1H, d, J=7.5Hz), 7.04 (1H, t, J=7.5Hz), 7.21 (1H, t, J=7.5Hz), 7.47 (1H, d, J=7.5Hz), 7.63 (1H, d, J=7.5Hz), 7.82 (1H, s), 7.97 (1H, d, J=7.5Hz)
MASS (m/z) : 409 (M^+ +1), 74 (bp)

(35) 1-(6-Chloro-3,4-methylenedioxybenzyl)-3-cyclobutanecarbonyl-2-propylindole-6-carboxamide

- 153 -

mp : 240-241°C

IR (KBr) : 1658, 1636, 1503, 1482, 1451 cm^{-1}

NMR (DMSO- d_6 , δ) : 0.94 (3H, t, $J=7\text{Hz}$), 1.49 (2H, sextet, $J=7\text{Hz}$), 1.79-1.90 (1H, m), 1.96-2.07 (1H, m), 2.24-2.33 (4H, m), 3.03 (2H, t, $J=7\text{Hz}$), 4.07 (1H, quintet, $J=7\text{Hz}$), 5.51 (2H, s), 5.65 (1H, s), 6.00 (2H, s), 7.24 (1H, s), 7.31 (1H, br s), 7.79 (1H, d, $J=7.5\text{Hz}$), 7.94 (1H, br s), 7.95 (1H, d, $J=7.5\text{Hz}$), 8.00 (1H, s)

10 MASS (m/z) : 453 (M^++1), 85 (bp)

(36) 1-(2-Chlorobenzyl)-3-cyclopentanecarbonyl-2-propylindole-6-carboxamide

mp : 201.5-202.5°C

15 IR (KBr) : 1654, 1607, 1447, 1437, 1387 cm^{-1}

NMR (CDCl_3 , δ) : 1.02 (3H, t, $J=7\text{Hz}$), 1.59-1.82 (6H, m), 1.99-2.07 (4H, m), 3.02-3.09 (2H, m), 3.79 (1H, quintet, $J=7\text{Hz}$), 5.52 (2H, s), 6.23 (1H, d, $J=7.5\text{Hz}$), 7.05 (1H, t, $J=7.5\text{Hz}$), 7.22 (1H, t, $J=7.5\text{Hz}$), 7.47 (1H, d, $J=7.5\text{Hz}$), 7.63 (1H, d, $J=7.5\text{Hz}$), 7.86 (1H, s), 8.04 (1H, d, $J=7.5\text{Hz}$)

20 MASS (m/z) : 423 (M^++1), 74 (bp)

(37) 1-(6-Chloro-3,4-methylenedioxybenzyl)-3-cyclopentanecarbonyl-2-propylindole-6-carboxamide

25 mp : 236-237°C

IR (KBr) : 1662, 1506, 1477 cm^{-1}

NMR (DMSO- d_6 , δ) : 0.93 (3H, t, $J=7\text{Hz}$), 1.40-1.50 (2H, m), 1.61-1.68 (4H, m), 1.81-1.95 (4H, m), 3.00 (2H, t, $J=7\text{Hz}$), 3.73-3.82 (1H, m), 5.50 (2H, s), 5.64 (1H, s), 6.00 (2H, s), 7.24 (1H, s), 7.30 (1H, br s), 7.80 (1H, d, $J=7.5\text{Hz}$), 7.95 (1H, br s), 8.00 (1H, d, $J=7.5\text{Hz}$), 8.01 (1H, s)

30 MASS (m/z) : 467 (M^++1), 85 (bp)

- 154 -

(38) 1-(2-Chlorobenzyl)-3-cyclohexanecarbonyl-2-propylindole-6-carboxamide

mp : 208-210°C

IR (KBr) : 1686, 1625, 1609, 1444, 1410 cm^{-1}

5 NMR (DMSO- d_6 , δ) : 0.90 (3H, t, $J=7\text{Hz}$), 1.19-1.30 (1H, m), 1.39-1.49 (6H, m), 1.67-1.93 (5H, m), 2.99 (2H, t, $J=7\text{Hz}$), 3.18-3.27 (1H, m), 5.61 (2H, s), 6.19 (1H, d, $J=7.5\text{Hz}$), 7.18 (1H, t, $J=7.5\text{Hz}$), 7.29 (1H, s), 7.32 (1H, t, $J=7.5\text{Hz}$), 7.58 (1H, d, $J=7.5\text{Hz}$), 7.80 (1H, d, $J=7.5\text{Hz}$), 7.90 (2H, d, $J=7.5\text{Hz}$), 9.00 (1H, s)

10 MASS (m/z) : 437 (M^++1), 85 (bp)

(39) 1-(6-Chloro-3,4-methylenedioxybenzyl)-3-cyclohexanecarbonyl-2-propylindole-6-carboxamide

15 mp : 209-211°C

IR (KBr) : 1623, 1611, 1506, 1391 cm^{-1}

20 NMR (DMSO- d_6 , δ) : 0.93 (3H, t, $J=7\text{Hz}$), 1.20-1.28 (1H, m), 1.39-1.51 (6H, m), 1.68-1.92 (5H, m), 2.96-3.01 (2H, m), 3.19-3.27 (1H, m), 5.52 (2H, s), 5.64 (1H, s), 6.00 (2H, s), 7.24 (1H, s), 7.31 (1H, br s), 7.85 (2H, AB, $J=7.5, 7.5\text{Hz}$), 7.96 (1H, br s), 8.01 (1H, s)

25 MASS (m/z) : 481 (M^++1), 85 (bp)

(40) 1-(2-Chlorobenzyl)-3-(3-methyl-2-butenoyl)-2-propylindole-6-carboxamide

mp : 187-188°C

IR (KBr) : 1680, 1648, 1614, 1598, 1446, 1384 cm^{-1}

30 NMR (DMSO- d_6 , δ) : 0.90 (3H, t, $J=7\text{Hz}$), 1.49 (2H, sextet, $J=7\text{Hz}$), 2.01 (3H, s), 2.10 (3H, s), 2.99 (2H, t, $J=7\text{Hz}$), 5.61 (2H, s), 6.19 (1H, d, $J=7.5\text{Hz}$), 6.66 (1H, s), 7.19 (1H, t, $J=7.5\text{Hz}$), 7.29 (1H, br s), 7.32 (1H, t, $J=7.5\text{Hz}$), 7.58 (1H, d, $J=7.5\text{Hz}$), 7.78 (1H, d, $J=7.5\text{Hz}$), 7.90 (1H, br s),

35

- 155 -

7.97 (2H, d, J=7.5Hz)

MASS (m/z) : 409 (M^+ +1), 85 (bp)

5 (41) 1-(6-Chloro-3,4-methylenedioxybenzyl)-3-(3-methyl-2-butenoyl)-2-propylindole-6-carboxamide

mp : 227-229°C

IR (KBr) : 1654, 1606, 1505, 1482, 1449, 1388 cm^{-1}

10 NMR (DMSO- d_6 , δ) : 0.94 (3H, t, J=7Hz), 1.50 (2H, sextet, J=7Hz), 2.01 (3H, s), 2.09 (3H, s), 3.00 (2H, t, J=7Hz), 5.50 (2H, s), 5.67 (1H, s), 6.00 (2H, s), 6.66 (1H, s), 7.25 (1H, s), 7.30 (1H, br s), 7.77 (1H, d, J=7.5Hz), 7.91-7.99 (3H, m)

MASS (m/z) : 453 (M^+ +1), 85 (bp)

15 (42) 1-(2-Chlorobenzyl)-3-(3-methoxybutanoyl)-2-propylindole-6-carboxamide

mp : 155-157°C

IR (KBr) : 1656, 1610, 1447, 1437, 1389 cm^{-1}

20 NMR (CDCl_3 , δ) : 1.03 (3H, t, J=7Hz), 1.34 (3H, d, J=7Hz), 1.63 (2H, sextet, J=7Hz), 3.01-3.09 (3H, m), 3.41 (3H, s), 3.47 (1H, dd, J=16, 7Hz), 4.14 (1H, sextet, J=7Hz), 5.51 (2H, s), 6.22 (1H, dd, J=7.5, 1Hz), 7.05 (1H, ddd, J=7.5, 7.5, 1Hz), 7.23 (1H, ddd, J=7.5, 7.5, 1Hz), 7.46 (1H, dd, J=7.5, 1Hz), 7.62 (1H, dd, J=7.5, 1Hz), 7.76 (1H, d, J=1Hz), 8.09 (1H, d, J=7.5Hz)

MASS (m/z) : 427 (M^+ +1), 74 (bp)

30 (43) 1-(6-Chloro-3,4-methylenedioxybenzyl)-3-(3-methoxybutanoyl)-2-propylindole-6-carboxamide

mp : 190-192.5°C

IR (KBr) : 1654, 1652, 1608, 1505, 1482 cm^{-1}

35 NMR (CDCl_3 , δ) : 1.04 (3H, t, J=7Hz), 1.33 (3H, d, J=7Hz), 1.62 (2H, sextet, J=7Hz), 3.00-3.09 (3H, m), 3.40 (3H, s), 3.45 (1H, dd, J=16, 7Hz), 4.12

- 156 -

(1H, sextet, J=7Hz), 5.40 (2H, s), 5.70 (1H, s),
5.90 (2H, s), 6.91 (1H, s), 7.61 (1H, d, J=7.5Hz),
7.88 (1H, s), 8.08 (1H, d, J=7.5Hz)

MASS (m/z) : 471 (M⁺+1), 74 (bp)

5

(44) 3-Acetyl-6-chloro-1-(2-chlorobenzyl)indole

NMR (CDCl₃, δ) : 2.49 (3H, s), 5.41 (2H, s), 6.75 (1H,
d, J=8Hz), 7.18 (1H, t, J=8Hz), 7.19 (1H, t,
J=8Hz), 7.2-7.33 (3H, m), 7.48 (1H, d, J=8Hz), 7.72
(1H, s), 8.33 (1H, d, J=8Hz)

10

Example 74

The following compounds described in (1) to (43) were
prepared in a similar manner to that of Example 2.

15

(1) 9-(2-Chlorobenzyl)-5-oxo-5,6,7,8-tetrahydrocarbazole-2-
carboxylic acid

NMR (CDCl₃, δ) : 2.24 (2H, m), 2.63 (2H, t, J=7Hz),
2.88 (2H, t, J=7Hz), 5.47 (2H, s), 6.36 (1H, d,
J=8Hz), 7.09 (1H, t, J=8Hz), 7.26 (1H, t, J=8Hz),
7.47 (1H, d, J=8Hz), 8.02 (1H, s), 8.04 (1H, d,
J=8Hz), 8.37 (1H, d, J=8Hz)

20

(2) 4-(2-Chlorobenzyl)-1-oxo-1,2,3,4-tetrahydrocyclopent-
[b]indole-6-carboxylic acid

25

NMR (DMSO-d₆, δ) : 2.87 (2H, m), 3.03 (2H, m), 5.64
(2H, s), 6.93 (1H, d, J=8Hz), 7.29 (1H, t, J=8Hz),
7.37 (1H, t, J=8Hz), 7.58 (1H, d, J=8Hz), 7.78 (1H,
d, J=8Hz), 7.83 (1H, d, J=8Hz), 8.05 (1H, s)

30

(3) 1-(2-Chlorobenzyl)-3-isobutyryl-2-propylindole-7-
carboxylic acid

NMR (CDCl₃, δ) : 1.03 (3H, t, J=7Hz), 1.29 (6H, d,
J=7Hz), 1.64 (2H, m), 3.03 (2H, m), 3.56 (1H, m),
5.75 (2H, s), 6.04 (1H, d, J=8Hz), 6.96 (1H, t,

35

- 157 -

J=8Hz), 7.12 (1H, t, J=8Hz), 7.29 (1H, t, J=8Hz),
7.33 (1H, d, J=8Hz), 7.67 (1H, d, J=8Hz) 8.19 (1H,
d, J=8Hz)

5 (4) 1-(2-Chlorobenzyl)-3-isobutyryl-2-propylindole-5-
carboxylic acid

NMR (DMSO-d₆, δ) : 0.90 (3H, t, J=8Hz), 1.19 (6H, d,
J=8Hz), 1.62 (2H, sextet, J=8Hz), 3.02 (2H, t,
J=8Hz), 3.51 (1H, septet, J=8Hz), 5.64 (2H, s),
10 6.28 (1H, d, J=8Hz), 7.18 (1H, t, J=8Hz), 7.32 (1H,
t, J=8Hz), 7.50 (1H, d, J=8Hz), 7.56 (1H, d,
J=8Hz), 7.78 (1H, d, J=8Hz), 8.58 (1H, s)

15 (5) 1-(6-Chloro-3,4-methylenedioxybenzyl)-3-isobutyryl-2-
propylindole-5-carboxylic acid

NMR (CDCl₃, δ) : 1.04 (3H, t, J=7Hz), 1.32 (6H, d,
J=7Hz), 1.62 (2H, sextet, J=7Hz), 3.06-3.12 (2H,
m), 3.66 (1H, septet, J=7Hz), 5.36 (2H, s), 5.74
(1H, s), 5.90 (2H, s), 6.93 (1H, s), 7.23 (1H, d,
20 J=8Hz), 7.96 (1H, dd, J=1, 8Hz), 8.76 (1H, d,
J=1Hz)

(6) 1-(2-Chlorobenzyl)-2-propylindole-4-carboxylic acid

NMR (CDCl₃, δ) : 1.03 (3H, t, J=7Hz), 1.80 (2H, m),
25 2.67 (2H, t, J=7Hz), 5.43 (2H, s), 6.19 (1H, d,
J=8Hz), 7.03 (1H, t, J=8Hz), 7.1-7.25 (3H, m), 7.34
(1H, d, J=8Hz), 7.41 (1H, d, J=8Hz), 7.99 (1H, d,
J=8Hz)

30 (7) 9-(2-Chlorobenzyl)-8-oxo-5,6,7,8-tetrahydrocarbazole-2-
carboxylic acid

NMR (CDCl₃, δ) : 2.28 (2H, m), 2.68 (2H, t, J=7Hz),
3.13 (2H, t, J=7Hz), 5.95 (2H, s), 6.27 (1H, d,
J=8Hz), 6.99 (1H, t, J=8Hz), 7.16 (1H, t, J=8Hz),
35 7.42 (1H, d, J=8Hz), 7.77 (1H, d, J=8Hz), 7.87 (1H,

- 158 -

d, J=8Hz), 8.03 (1H, s)

(8) 9-(6-Chloro-3,4-methylenedioxybenzyl)-8-oxo-5,6,7,8-tetrahydrocarbazole-2-carboxylic acid

5 NMR (DMSO-d₆, δ) : 2.19 (2H, m), 2.63 (2H, t, J=7Hz),
3.06 (2H, t, J=7Hz), 5.70 (1H, s), 5.82 (2H, s),
5.96 (2H, s), 7.16 (1H, s), 7.73 (1H, d, J=8Hz),
7.88 (1H, d, J=8Hz), 7.98 (1H, s)

10 (9) 1-(4-Bromo-2-chlorobenzyl)-3-isobutyryl-2-propylindole-6-carboxylic acid

mp : 234-235°C

IR (KBr) : 1677, 1648, 1418 cm⁻¹

15 NMR (CDCl₃, δ) : 1.04 (3H, t, J=7Hz), 1.30 (6H, d,
J=7Hz), 1.54-1.64 (2H, m), 3.02-3.08 (2H, m), 3.50-
3.61 (1H, m), 5.44 (2H, s), 6.10 (1H, t, J=8Hz),
7.18 (1H, dd, J=8, 1Hz), 7.65 (1H, d, J=1Hz), 7.94-
8.05 (3H, m)

MASS (m/z) : 476 (M⁺)

20

(10) 1-(2-Chlorobenzyl)-3-morpholinoacetyl-2-propylindole-6-carboxylic acid

IR (KBr) : 1652, 1441, 1115 cm⁻¹

25 NMR (CDCl₃, δ) : 1.02 (3H, t, J=7Hz), 1.60 (2H,
sextet, J=7Hz), 2.74 (4H, t, J=6.5Hz), 3.03-3.09
(2H, m), 3.86 (4H, t, J=6.5Hz), 3.93 (2H, s), 5.52
(2H, s), 6.25 (1H, d, J=7.5Hz), 7.05 (1H, t,
J=7.5Hz), 7.22 (1H, t, J=7.5Hz), 7.47 (1H, d,
J=7.5Hz), 7.90-8.01 (3H, m)

30 MASS (m/z) : 455 (M⁺-1)

(11) 1-(2-Chlorobenzyl)-3-(N,N-dimethylcarbamoyl)-2-propylindole-6-carboxylic acid

IR (KBr) : 1704, 1596, 1219 cm⁻¹

35 NMR (CDCl₃, δ) : 0.93 (3H, t, J=7Hz), 1.52-1.63 (2H,

- 159 -

m), 2.80-2.90 (2H, m), 3.13 (6H, s), 5.48 (2H, s),
6.30 (1H, d, J=7.5Hz), 7.04 (1H, t, J=7.5Hz), 7.20
(1H, t, J=7.5Hz), 7.44 (1H, d, J=7.5Hz), 7.50 (1H,
d, J=7.5Hz), 7.91 (1H, d, J=7.5Hz), 7.96 (1H, s)

5 MASS (m/z) : 399 (M^+-1)

(12) 1-(2-Chlorobenzyl)-3-morpholinocarbonyl-2-propylindole-
6-carboxylic acid

IR (KBr) : 3410, 1615, 1540, 1444, 1400 cm^{-1}

10 NMR (DMSO- d_6 , δ) : 0.84 (3H, t, J=7Hz), 1.39-1.49 (2H,
m), 2.76-2.84 (2H, m), 3.56 (6H, br s), 3.68 (2H,
br s), 5.52 (2H, s), 6.24 (1H, d, J=7.5Hz), 7.16
(1H, t, J=7.5Hz), 7.29 (1H, t, J=7.5Hz), 7.40 (1H,
d, J=7.5Hz), 7.54 (1H, d, J=7.5Hz), 7.79 (1H, s),
15 7.81 (1H, s)

MASS (m/z) : 439 (M^+-1), 99 (bp)

(13) 1-(2-Chlorobenzyl)-2-propylindole-3,6-dicarboxylic acid
mp : 241-243°C (dec.)

20 IR (KBr) : 1669, 1525, 1443, 1385 cm^{-1}

NMR (DMSO- d_6 , δ) : 0.90 (3H, t, J=7Hz), 1.44-1.55 (2H,
m), 3.12 (2H, t, J=7Hz), 5.56 (2H, s), 6.22 (1H, d,
J=7.5Hz), 7.17 (1H, t, J=7.5Hz), 7.30 (1H, t,
J=7.5Hz), 7.57 (1H, d, J=7.5Hz), 7.79 (1H, s), 8.06
25 (1H, d, J=7.5Hz)

MASS (m/z) : 370 (M^+-1), 99 (bp)

(14) 1-(2-Chlorobenzyl)-2-ethyl-3-formylindole-6-carboxylic
acid

30 mp : 241-242°C (dec.)

IR (KBr) : 1675, 1650, 1295 cm^{-1}

NMR (CDCl_3 , δ) : 1.29 (3H, t, J=7Hz), 3.09 (2H, q,
J=7Hz), 5.52 (2H, s), 6.30 (1H, d, J=7.5Hz), 7.08
(1H, t, J=7.5Hz), 7.25 (1H, t, J=7.5Hz), 7.49 (1H,
35 d, J=7.5Hz), 7.97 (1H, s), 8.03 (1H, d, J=7.5Hz),

- 160 -

8.35 (1H, d, J=7.5Hz), 10.25 (1H, s)

MASS (m/z) : 340 (M^+-1)

- (15) 1-(2-Chlorobenzyl)-3-formylindole-6-carboxylic acid
5 NMR (DMSO- d_6 , δ) : 5.73 (2H, s), 6.96 (1H, d, J=8Hz),
7.23-7.4 (2H, m), 7.56 (1H, d, J=8Hz), 7.89 (1H, d,
J=8Hz), 8.15 (1H, s), 8.21 (1H, s), 8.54 (1H, s),
10.0 (1H, s)
- 10 (16) 3-Acetyl-1-(2-chlorobenzyl)-2-methylindole-6-carboxylic
acid
NMR (CDCl₃, δ) : 2.71 (3H, s), 2.76 (3H, s), 5.50 (2H,
s), 6.22 (1H, d, J=8Hz), 7.05 (1H, t, J=8Hz), 7.22
(1H, t, J=8Hz), 7.47 (1H, d, J=8Hz), 7.95-8.15 (3H,
15 m), 8.08 (1H, d, J=8Hz)
- (17) 1-(2-Chlorobenzyl)-2-methyl-3-propionylindole-6-
carboxylic acid
NMR (DMSO- d_6 , δ) : 1.14 (3H, t, J=7Hz), 2.69 (3H, s),
20 3.04 (2H, q, J=7Hz), 5.67 (2H, s), 6.24 (1H, d,
J=8Hz), 7.18 (1H, d, J=8Hz), 7.22 (1H, t, J=8Hz),
7.58 (1H, d, J=8Hz), 7.83 (1H, d, J=8Hz), 7.99 (1H,
s), 8.16 (1H, d, J=8Hz)
- 25 (18) 1-(2-Chlorobenzo[b]thiophen-3-ylmethyl)-3-isobutyryl-2-
methylindole-6-carboxylic acid
NMR (CDCl₃, δ) : 1.25 (6H, d, J=7Hz), 2.71 (3H, s),
3.50 (1H, m), 5.61 (2H, s), 6.99 (1H, d, J=8Hz),
7.12 (1H, t, J=8Hz), 7.28 (1H, t, J=8Hz), 7.68 (1H,
30 d, J=8Hz), 7.95-8.02 (2H, m), 8.23 (1H, s)
- (19) 1-(Benzothiazol-2-ylmethyl)-2-ethyl-3-isobutyrylindole-
6-carboxylic acid
NMR (CDCl₃, δ) : 1.28 (3H, t, J=7Hz), 1.30 (6H, d,
35 J=7Hz), 3.24 (2H, q, J=7Hz), 3.58 (1H, m), 5.86

- 161 -

(2H, s), 7.39 (1H, t, J=8Hz), 7.52 (1H, t, J=8Hz),
7.87 (1H, d, J=8Hz), 7.9-8.06 (3H, m), 8.20 (1H, s)

(20) 1-(Benzo[b]thiophen-5-ylmethyl)-3-isobutyryl-2-propylindole-6-carboxylic acid

5 NMR (CDCl₃, δ) : 1.02 (3H, t, J=7Hz), 1.32 (6H, d, J=7Hz), 1.63 (2H, m), 3.14 (2H, m), 3.57 (1H, m), 5.58 (2H, s), 7.04 (1H, d, J=8Hz), 7.19 (1H, d, J=6Hz), 7.31 (1H, s), 7.43 (1H, d, J=6Hz), 7.81
10 (1H, d, J=8Hz), 7.9-8.02 (2H, m), 8.08 (1H, s)

(21) 1-(2,4-Dichlorobenzyl)-3-isobutyryl-2-propylindole-6-carboxylic acid

15 NMR (DMSO-d₆, δ) : 0.92 (3H, t, J=7Hz), 1.18 (6H, d, J=7Hz), 1.46 (2H, sextet, J=7Hz), 3.02-3.07 (2H, m), 3.54 (2H, septet, J=7Hz), 5.68 (2H, s), 6.27 (1H, d, J=8Hz), 7.28 (1H, dd, J=2, 8Hz), 7.76 (1H, d, J=2Hz), 7.84 (1H, d, J=8Hz), 7.96 (1H, s), 8.01 (1H, d, J=8Hz)

20

(22) 3-Isobutyryl-2-propyl-1-(3-pyridylmethyl)indole-6-carboxylic acid

25 NMR (CDCl₃, δ) : 1.04 (3H, t, J=7Hz), 1.30 (6H, d, J=7Hz), 1.63 (2H, sextet, J=7Hz), 3.15 (2H, t, J=7Hz), 3.57 (2H, septet, J=7Hz), 5.51 (2H, s), 7.19-7.28 (2H, m), 7.95-8.01 (2H, m), 8.04 (1H, s), 8.52-8.56 (2H, m)

(23) 3-Isobutyryl-2-propyl-1-(1-naphthylmethyl)indole-6-carboxylic acid

30 NMR (DMSO-d₆, δ) : 0.86 (3H, t, J=7Hz), 1.22 (6H, d, J=7Hz), 1.52 (2H, sextet, J=7Hz), 3.05-3.10 (2H, m), 3.60 (1H, septet, J=7Hz), 6.15 (1H, d, J=8Hz), 6.17 (2H, s), 7.28 (1H, t, J=8Hz), 7.64 (1H, t, J=8Hz), 7.72 (1H, t, J=8Hz), 7.84 (2H, d, J=8Hz),
35

- 162 -

7.92 (1H, s), 8.12 (1H, d, J=8Hz), 8.15 (1H, d, J=8Hz), 8.36 (1H, d, J=8Hz)

5 (24) 3-Isobutyryl-2-propyl-1-(2-naphthylmethyl)indole-6-carboxylic acid

NMR (DMSO-d₆, δ) : 0.92 (3H, t, J=7Hz), 1.19 (6H, d, J=7Hz), 1.48 (2H, sextet, J=7Hz), 3.14-3.18 (2H, m), 3.57 (1H, septet, J=7Hz), 5.81 (2H, s), 7.20 (1H, d, J=8Hz), 7.45-7.52 (3H, m), 7.76-7.90 (4H, m), 8.02 (1H, d, J=8Hz), 8.08 (1H, s)

10

(25) 1-Allyl-3-isobutyryl-2-propylindole-6-carboxylic acid

NMR (CDCl₃, δ) : 1.08 (3H, t, J=7Hz), 1.28 (6H, d, J=7Hz), 1.69 (2H, m), 3.13 (2H, m), 3.56 (1H, m), 4.88 (2H, m), 4.90 (1H, m), 5.23 (1H, m), 5.98 (1H, m), 7.94 (1H, d, J=8Hz), 8.02 (1H, d, J=8Hz), 8.13 (1H, s)

15

20 (26) 1-(2-Chlorobenzyl)-3-isobutyryl-2-(1-propenyl)indole-6-carboxylic acid

NMR (CDCl₃, δ) : 1.26 (6H, d, J=7Hz), 1.93 (3H, d, J=7Hz), 3.51 (1H, m), 5.50 (2H, s), 5.92 (1H, m), 6.44 (1H, d, J=8Hz), 6.74 (1H, d, J=16Hz), 7.09 (1H, t, J=8Hz), 7.23 (1H, t, J=8Hz), 7.48 (1H, d, J=8Hz), 7.92 (1H, s), 8.02 (1H, d, J=8Hz), 8.21 (1H, d, J=8Hz)

25

(27) 1-(2-Chlorobenzyl)-2-(1-hydroxypropyl)-3-isobutyrylindole-6-carboxylic acid

NMR (CDCl₃, δ) : 0.92 (3H, t, J=7Hz), 1.29 (3H, d, J=7Hz), 1.36 (3H, d, J=7Hz), 1.52 (1H, m), 1.88 (1H, m), 3.70 (1H, m), 4.73 (1H, m), 5.51 (1H, d, J=17Hz), 5.69 (1H, d, J=17Hz), 6.44 (1H, d, J=8Hz), 7.09 (1H, t, J=8Hz), 7.23 (1H, t, J=8Hz), 7.45 (1H, d, J=8Hz), 7.9-8.1 (3H, m)

30

35

- 163 -

(28) 1-(2-Chlorobenzyl)-3-(3,3-dimethylbutanoyl)indole-6-carboxylic acid

NMR (CDCl₃, δ) : 1.08 (9H, s), 2.70 (2H, s), 5.52 (2H, s), 6.77 (1H, d, J=8Hz), 7.17 (1H, t, J=8Hz), 7.28 (1H, t, J=8Hz), 7.47 (1H, d, J=8Hz), 7.86 (1H, s), 8.03 (1H, d, J=8Hz), 8.12 (1H, s), 8.53 (1H, d, J=8Hz)

(29) 1-(6-Chloro-3,4-methylenedioxybenzyl)-3-methoxyacetyl-2-propylindole-6-carboxylic acid

NMR (CDCl₃, δ) : 0.96 (3H, t, J=7Hz), 1.45-1.58 (2H, m), 3.10 (2H, t, J=7Hz), 3.40 (3H, s), 4.69 (2H, s), 5.55 (2H, s), 5.76 (1H, s), 5.98 (2H, s), 7.23 (1H, s), 7.82 (1H, d, J=8Hz), 7.94 (1H, s), 7.96 (1H, d, J=8Hz)

(30) 1-(2-Chlorobenzyl)-3-ethoxyacetyl-2-propylindole-6-carboxylic acid

NMR (DMSO-d₆, δ) : 0.94 (3H, t, J=7Hz), 1.17 (3H, t, J=7Hz), 1.48 (2H, sextet, J=7Hz), 3.08 (3H, t, J=7Hz), 3.62 (2H, q, J=7Hz), 4.74 (2H, s), 5.68 (2H, s), 6.28 (1H, d, J=8Hz), 7.18 (1H, t, J=8Hz), 7.32 (1H, t, J=8Hz), 7.56 (1H, d, J=8Hz), 7.82 (1H, d, J=8Hz), 7.96 (1H, s), 7.98 (1H, d, J=8Hz)

(31) 1-(2-Chlorobenzyl)-3-isobutyryl-2-propylindol-6-ylacetic acid

IR (KBr) : 1715, 1650 cm⁻¹

NMR (CDCl₃, δ) : 1.00 (3H, t, J=7Hz), 1.30 (6H, d, J=7Hz), 1.54-1.66 (2H, m), 3.00-3.08 (2H, m), 3.50-3.62 (1H, m), 3.71 (2H, s), 5.47 (2H, s), 6.30 (1H, d, J=7.5Hz), 7.01-7.08 (2H, m), 7.19-7.25 (2H, m), 7.45 (1H, d, J=7.5Hz), 7.89 (1H, d, J=7.5Hz)

MASS (m/z) : 412 (M⁺+1), 74 (bp)

- 164 -

(32) 1-(6-Chloro-3,4-methylenedioxybenzyl)-3-isobutyryl-2-propylindole-6-ylacetic acid

mp : 81-83°C

IR (KBr) : 1715, 1650 cm⁻¹

5 NMR (CDCl₃, δ) : 1.02 (3H, t, J=7Hz), 1.29 (6H, d, J=7Hz), 1.54-1.67 (2H, m), 3.01-3.07 (2H, m), 3.51-3.60 (1H, m), 3.75 (2H, s), 5.33 (2H, s), 5.79 (1H, s), 5.89 (2H, s), 6.91 (1H, s), 7.12 (1H, s), 7.21 (1H, d, J=7.5Hz), 7.89 (1H, d, J=7.5Hz)

10 MASS (m/z) : 456 (M⁺+1), 74 (bp)

(33) 1-(2-Chlorobenzyl)-2-propylindole-6-carboxylic acid

15 NMR (CDCl₃, δ) : 1.02 (3H, t, J=7Hz), 1.74 (2H, m), 2.61 (2H, t, J=7Hz), 5.42 (2H, s), 6.19 (1H, d, J=8Hz), 6.46 (1H, s), 7.02 (1H, t, J=8Hz), 7.18 (1H, t, J=8Hz), 7.43 (1H, d, J=8Hz), 7.61 (1H, d, J=8Hz), 7.85 (1H, d, J=8Hz), 7.95 (1H, s)

(34) 1-(2-Bromobenzyl)-2-propylindole-6-carboxylic acid

20 NMR (CDCl₃, δ) : 1.00 (3H, t, J=7Hz), 1.73 (2H, m), 2.61 (2H, t, J=7Hz), 5.37 (2H, s), 6.12 (1H, d, J=8Hz), 6.46 (1H, s), 7.0-7.18 (2H, m), 7.61 (1H, d, J=8Hz), 7.85 (1H, d, J=8Hz), 7.96 (1H, s)

25 (35) 2-Acetyl-1-(2-chlorobenzyl)-3-methylindole-6-carboxylic acid

30 NMR (DMSO-d₆, δ) : 2.62 (3H, s), 2.69 (3H, s), 5.82 (2H, s), 6.10 (1H, d, J=8Hz), 7.09 (1H, t, J=8Hz), 7.24 (1H, t, J=8Hz), 7.51 (1H, d, J=8Hz), 7.72 (1H, d, J=8Hz), 7.93 (1H, d, J=8Hz), 7.96 (1H, s)

(36) 2-Chloro-1-(2-chlorobenzyl)-3-ethylindole-6-carboxylic acid

35 NMR (CDCl₃, δ) : 1.30 (3H, t, J=7Hz), 2.84 (2H, q, J=7Hz), 5.50 (2H, s), 6.29 (1H, d, J=8Hz), 7.06

- 165 -

(1H, t, J=8Hz), 7.19 (1H, t, J=8Hz), 7.43 (1H, d, J=8Hz), 7.63 (1H, d, J=8Hz), 7.88 (1H, d, J=8Hz), 7.93 (1H, s)

5 (37) 1-(2-Chlorobenzyl)-2-propionyl-3-propylindole-6-carboxylic acid

NMR (CDCl₃, δ) : 1.06 (3H, t, J=7Hz), 1.14 (3H, t, J=7Hz), 1.76 (2H, m), 2.94 (2H, q, J=7Hz), 3.09 (2H, m), 5.72 (2H, s), 6.27 (1H, d, J=8Hz), 6.99 (1H, t, J=8Hz), 7.14 (1H, t, J=8Hz), 7.39 (1H, d, J=8Hz), 7.78 (1H, d, J=8Hz), 7.87 (1H, d, J=8Hz), 8.02 (1H, s)

15 (38) 1-(2-Chlorobenzyl)-2-isobutyryl-3-propylindole-6-carboxylic acid

NMR (CDCl₃, δ) : 1.03 (3H, t, J=7Hz), 1.11 (6H, d, J=7Hz), 1.76 (2H, m), 3.03 (2H, m), 3.34 (1H, m), 5.64 (2H, s), 6.30 (1H, d, J=8Hz), 7.01 (1H, t, J=8Hz), 7.14 (1H, t, J=8Hz), 7.39 (1H, d, J=8Hz), 7.78 (1H, d, J=8Hz), 7.88 (1H, d, J=8Hz), 8.02 (1H, s)

(39) 1-(2-Chlorobenzyl)-3-(3-oxo-1-butenyl)indole-6-carboxylic acid

25 NMR (DMSO-d₆, δ) : 2.32 (3H, s), 5.67 (2H, s), 6.76 (1H, d, J=15Hz), 6.86 (1H, d, J=8Hz), 7.28 (1H, t, J=8Hz), 7.37 (1H, t, J=8Hz), 7.54 (1H, d, J=8Hz), 7.79 (1H, d, J=8Hz), 7.83 (1H, d, J=15Hz), 8.08 (1H, d, J=8Hz), 8.11 (1H, s), 8.21 (1H, s)

30

(40) 4-(2-Chlorobenzyl)-3-oxo-1,2,3,4-tetrahydrocyclopent[b]-indole-6-carboxylic acid

NMR (CDCl₃, δ) : 3.07 (2H, m), 3.17 (2H, m), 5.72 (2H, s), 6.58 (1H, d, J=8Hz), 7.06 (1H, t, J=8Hz), 7.18 (1H, t, J=8Hz), 7.40 (1H, d, J=8Hz), 7.78 (1H, d,

35

- 166 -

J=8Hz), 7.89 (1H, d, J=8Hz), 8.09 (1H, s)

(41) 4-(6-Chloro-3,4-methylenedioxybenzyl)-3-oxo-1,2,3,4-tetrahydrocyclopent[b]indole-6-carboxylic acid

5 NMR (CDCl₃, δ) : 3.07 (2H, m), 3.16 (2H, m), 5.61 (2H, s), 5.88 (2H, s), 6.10 (1H, s), 6.88 (1H, s), 7.78 (1H, d, J=8Hz), 7.88 (1H, d, J=8Hz), 8.12 (1H, s)

(42) 1-(2-Chlorobenzyl)-3-nitro-2-propylindole-6-carboxylic acid

10 NMR (DMSO-d₆, δ) : 0.95 (3H, t, J=7Hz), 1.55 (2H, sextet, J=7Hz), 3.18-3.22 (2H, m), 5.78 (2H, s), 6.52 (1H, d, J=8Hz), 7.22 (1H, t, J=8Hz), 7.33 (1H, t, J=8Hz), 7.58 (1H, d, J=8Hz), 7.97 (1H, d, J=8Hz), 8.08 (1H, s) 8.27 (1H, d, J=8Hz)

(43) 1-(2-Chloro-4-carboxybenzyl)-3-isobutyryl-2-propylindole-6-carboxamide

20 NMR (DMSO-d₆, δ) : 0.90 (3H, t, J=7Hz), 1.18 (6H, d, J=7Hz), 1.46 (2H, sextet, J=7Hz), 3.00-3.05 (2H, m), 3.55 (1H, septet, J=7Hz), 5.68 (2H, s), 6.33 (1H, d, J=8Hz), 7.30 (1H, s), 7.72 (1H, dd, J=2, 8Hz), 7.92 (1H, s), 7.95-7.99 (2H, m), 8.03 (1H, d, J=8Hz)

25

Example 75

The following compounds described in (1) to (41) were prepared in a similar manner to that of Example 3.

30 (1) 9-(2-Chlorobenzyl)-5-oxo-5,6,7,8-tetrahydrocarbazole-2-carboxamide

mp : 295°C (dec.)

35 NMR (DMSO-d₆, δ) : 2.13 (2H, m), 2.48 (2H, t, J=7Hz), 2.92 (2H, t, J=7Hz), 5.62 (2H, s), 6.41 (1H, d, J=8Hz), 7.21 (1H, t, J=8Hz), 7.27 (1H, br s), 7.33

- 167 -

(1H, t, J=8Hz), 7.57 (1H, d, J=8Hz), 7.79 (1H, d, J=8Hz), 7.92 (1H, br s), 8.02 (1H, s), 8.08 (1H, d, J=8Hz)

- 5 (2) 4-(2-Chlorobenzyl)-1-oxo-1,2,3,4-tetrahydrocyclopent[b]-indole-6-carboxamide

mp : >300°C

10 NMR (DMSO-d₆, δ) : 2.88 (2H, m), 2.97 (2H, m), 5.61 (2H, s), 6.81 (1H, d, J=8Hz), 7.27 (1H, t, J=8Hz), 7.36 (1H, br s), 7.38 (1H, t, J=8Hz), 7.57 (1H, d, J=8Hz), 7.76 (1H, d, J=8Hz), 7.79 (1H, d, J=8Hz), 7.96 (1H, br s), 8.05 (1H, s)

- 15 (3) 1-(2-Chlorobenzyl)-3-isobutyryl-2-propylindole-7-carboxamide

mp : 181-183°C

20 NMR (CDCl₃, δ) : 1.03 (3H, t, J=7Hz), 1.27 (6H, d, J=7Hz), 1.61 (2H, m), 3.02 (2H, m), 3.53 (1H, m), 5.34 (1H, br s), 5.46 (1H, br s), 5.69 (2H, s), 5.99 (1H, d, J=8Hz), 6.96 (1H, t, J=8Hz), 7.14 (1H, t, J=8Hz), 7.15-7.25 (2H, m), 7.37 (1H, d, J=8Hz), 8.07 (1H, m)

- 25 (4) 1-(2-Chlorobenzyl)-3-isobutyryl-2-propylindole-5-carboxamide

30 NMR (CDCl₃, δ) : 1.03 (3H, t, J=8Hz), 1.32 (6H, d, J=8Hz), 1.64 (2H, sextet, J=8Hz), 3.06 (2H, t, J=8Hz), 3.62 (1H, septet, J=8Hz), 5.46 (2H, s), 6.26 (1H, d, J=8Hz), 7.05 (1H, t, J=8Hz), 7.20 (1H, t, J=8Hz), 7.2 (1H, d, J=8Hz), 7.47 (1H, d, J=8Hz), 7.65 (1H, d, J=8Hz), 8.55 (1H, s)

- 35 (5) 1-(6-Chloro-3,4-methylenedioxybenzyl)-3-isobutyryl-2-propylindole-5-carboxamide

NMR (CDCl₃, δ) : 1.05 (3H, t, J=7Hz), 1.32 (6H, d,

- 168 -

J=7Hz), 1.60-1.72 (2H, m), 3.04-3.10 (2H, m), 3.59 (1H, septet, J=7Hz), 5.38 (2H, s), 5.74 (1H, s), 5.92 (2H, s), 6.92 (1H, s), 7.22 (1H, d, J=8Hz), 7.66 (1H, dd, J=1, 8Hz), 8.50 (1H, d, J=1Hz)

5

(6) 1-(2-Chlorobenzyl)-2-propylindole-4-carboxamide

mp : 198-200°C

NMR (CDCl₃, δ) : 1.02 (3H, t, J=7Hz), 1.76 (2H, m), 2.66 (2H, t, J=7Hz), 5.41 (2H, s), 6.18 (1H, d, J=8Hz), 6.85 (1H, s), 7.1-7.3 (3H, m), 7.43 (1H, d, J=8Hz), 7.52 (1H, d, J=8Hz)

10

(7) 9-(2-Chlorobenzyl)-8-oxo-5,6,7,8-tetrahydrocarbazole-2-carboxamide

mp : 255°C (dec.)

NMR (DMSO-d₆, δ) : 2.18 (2H, m), 2.56 (2H, t, J=7Hz), 3.07 (2H, t, J=7Hz), 5.88 (2H, s), 6.08 (1H, d, J=8Hz), 7.11 (1H, t, J=8Hz), 7.25 (1H, t, J=8Hz), 7.36 (1H, br s), 7.52 (1H, d, J=8Hz), 7.72 (1H, d, J=8Hz), 7.85 (1H, d, J=8Hz), 8.02 (2H, m)

20

(8) 9-(6-Chloro-3,4-methylenedioxybenzyl)-8-oxo-5,6,7,8-tetrahydrocarbazole-2-carboxamide

mp : 270°C (dec.)

NMR (DMSO-d₆, δ) : 2.17 (2H, m), 2.58 (2H, t, J=7Hz), 3.08 (2H, t, J=7Hz), 5.52 (1H, s), 5.78 (2H, s), 5.96 (2H, s), 7.17 (1H, s), 7.40 (1H, br s), 7.71 (1H, d, J=8Hz), 7.86 (1H, d, J=8Hz), 7.96 (1H, s), 8.01 (1H, br s)

30

(9) 1-(4-Bromo-2-chlorobenzyl)-3-isobutyryl-2-propylindole-6-carboxamide

mp : 199-201°C

IR (KBr) : 3382, 1654, 1619, 1488, 1404 cm⁻¹

NMR (CDCl₃, δ) : 1.04 (3H, t, J=7Hz), 1.30 (6H, d,

35

- 169 -

J=7Hz), 1.54-1.66 (2H, m), 3.00-3.05 (2H, m), 3.50-3.60 (1H, m), 5.45 (2H, s), 6.09 (1H, t, J=7.5Hz), 7.17 (1H, dd, J=7.5, 2Hz), 7.62 (1H, dd, J=7.5, 2Hz), 7.65 (1H, d, J=2Hz), 7.83 (1H, s), 7.99 (1H, d, J=7.5Hz)

MASS (m/z) : 477 ($M^+ + 2$)

(10) 1-(2-Chlorobenzyl)-3-morpholinoacetyl-2-propylindole-6-carboxamide

IR (KBr) : 1654, 1616, 1452 cm^{-1}

NMR (CDCl_3 , δ) : 1.02 (3H, t, J=7Hz), 1.58-1.68 (2H, m), 2.73 (4H, t, J=6.5Hz), 3.05-3.10 (2H, m), 3.84 (4H, t, J=6.5Hz), 3.89 (2H, s), 5.51 (2H, s), 6.23 (1H, d, J=7.5Hz), 7.05 (1H, t, J=7.5Hz), 7.22 (1H, t, J=7.5Hz), 7.46 (1H, d, J=7.5Hz), 7.64 (1H, d, J=7.5Hz), 7.84 (1H, s), 7.98 (1H, d, J=7.5Hz)

MASS (m/z) : 454 ($M^+ + 1$)

(11) Methyl 1-(2-chlorobenzyl)-3-(N,N-dimethylcarbamoyl)-2-propylindole-6-carboxylate

IR (KBr) : 1703, 1610 cm^{-1}

NMR (CDCl_3 , δ) : 0.94 (3H, t, J=7Hz), 1.56-1.63 (2H, m), 2.76-2.87 (2H, m), 3.11 (6H, br s), 3.90 (3H, s), 5.49 (2H, s), 6.29 (1H, d, J=7.5Hz), 7.04 (1H, t, J=7.5Hz), 7.21 (1H, t, J=7.5Hz), 7.45 (1H, d, J=7.5Hz), 7.49 (1H, d, J=7.5Hz), 7.86 (1H, d, J=7.5Hz), 7.90 (1H, s)

MASS (m/z) : 413 ($M^+ + 1$)

(12) Methyl 1-(2-chlorobenzyl)-3-(morpholinocarbonyl)-2-propylindole-6-carboxylate

IR (KBr) : 1715, 1617, 1277, 1227 cm^{-1}

NMR (CDCl_3 , δ) : 0.85 (3H, t, J=7Hz), 1.56-1.63 (2H, m), 2.82-2.90 (2H, m), 3.69 (6H, br s), 3.77 (2H, br s), 3.90 (3H, s), 5.48 (2H, s), 6.29 (1H, d,

- 170 -

J=7.5Hz), 7.04 (1H, t, J=7.5Hz), 7.21 (1H, ddd, J=7.5, 7.5, 2Hz), 7.45 (1H, d, J=7.5Hz), 7.54 (1H, d, J=7.5Hz), 7.88 (1H, s), 7.91 (1H, d, J=2Hz)
MASS (m/z) : 455 (M^+ +1), 76 (bp)

5

(13) 6-Carbamoyl-1-(2-chlorobenzyl)-N,N-dimethyl-2-propylindole-3-carboxamide

mp : 213-214°C

IR (KBr) : 1676, 1601 cm^{-1}

10 NMR (CDCl_3 , δ) : 0.93 (3H, t, J=7Hz), 1.52-1.62 (2H, m), 2.76-2.86 (2H, m), 3.12 (6H, br s), 5.47 (2H, s), 6.27 (1H, d, J=7.5Hz), 7.03 (1H, t, J=7.5Hz), 7.20 (1H, t, J=7.5Hz), 7.44 (1H, d, J=7.5Hz), 7.49-7.54 (2H, m), 7.78 (1H, s)

15 MASS (m/z) : 398 (M^+ +1), 76 (bp)

(14) 1-(2-Chlorobenzyl)-3-(morpholinocarbonyl)-2-propylindole-6-carboxamide

mp : 229-230°C

20 IR (KBr) : 3448, 3359, 3326, 1675, 1606 cm^{-1}

NMR (CDCl_3 , δ) : 0.95 (3H, t, J=7Hz), 1.57-1.62 (2H, m), 2.82-2.89 (2H, m), 3.69 (6H, br s), 3.78 (2H, br s), 5.49 (2H, s), 6.28 (1H, d, J=7.5Hz), 7.04 (1H, t, J=7.5Hz), 7.21 (1H, t, J=7.5Hz), 7.45 (1H, t, J=7.5Hz), 7.55 (2H, s), 7.80 (1H, s)

25

MASS (m/z) : 440 (M^+ +1), 76 (bp)

(15) 1-(2-Chlorobenzyl)-2-propylindole-3,6-dicarboxamide

mp : 296°C (dec.)

30 IR (KBr) : 3376, 3188, 1644, 1613 cm^{-1}

NMR ($\text{DMSO}-d_6$, δ) : 0.88 (3H, t, J=7Hz), 1.40-1.51 (2H, m), 2.98 (2H, t, J=7Hz), 5.57 (2H, s), 6.17 (1H, d, J=7.5Hz), 7.14-7.35 (6H, m), 7.58 (1H, d, J=7.5Hz), 7.73 (1H, d, J=7.5Hz), 7.83-7.89 (1H, m), 7.95 (1H, s)

35

- 171 -

MASS (m/z) : 370 ($M^+ + 1$), 86 (bp)

(16) 1-(2-Chlorobenzyl)-2-ethyl-3-formylindole-6-carboxamide

mp : 260-261°C

5 IR (KBr) : 3400, 1685, 1635, 1615, 1390 cm^{-1}

NMR (CDCl_3 , δ) : 1.29 (3H, t, $J=7\text{Hz}$), 3.08 (2H, q, $J=7\text{Hz}$), 5.52 (2H, s), 6.29 (1H, d, $J=7.5\text{Hz}$), 7.07 (1H, t, $J=7.5\text{Hz}$), 7.24 (1H, t, $J=7.5\text{Hz}$), 7.49 (1H, d, $J=7.5\text{Hz}$), 7.69 (1H, d, $J=7.5\text{Hz}$), 7.86 (1H, s),
10 8.35 (1H, d, $J=7.5\text{Hz}$), 10.24 (1H, s)

MASS (m/z) : 341 ($M^+ + 1$)

(17) 1-(2-Chlorobenzoyl)-3-isobutyryl-2-propylindole-6-carboxamide

15 mp : 125-126.5°C

IR (KBr) : 1700, 1650 cm^{-1}

NMR (CDCl_3 , δ) : 0.90 (3H, t, $J=7\text{Hz}$), 1.28 (6H, d, $J=7\text{Hz}$), 1.61-1.74 (2H, m), 2.98-3.05 (2H, m), 3.40-3.49 (1H, m), 7.48-7.53 (3H, m), 7.59-7.65 (2H, m),
20 7.79 (2H, AB, $J=8, 7.5\text{Hz}$)

MASS (m/z) : 411 ($M^+ + 1$), 76 (bp)

(18) 1-(2-Chlorobenzyl)-3-formylindole-6-carboxamide

mp : 237-240°C

NMR ($\text{DMSO}-d_6$, δ) : 5.68 (2H, s), 6.86 (1H, d, $J=8\text{Hz}$),
25 6.25-6.4 (3H, m), 7.58 (1H, d, $J=8\text{Hz}$), 7.84 (1H, d, $J=8\text{Hz}$), 7.98 (1H, br s), 8.14 (1H, s), 8.17 (1H, d, $J=8\text{Hz}$), 8.46 (1H, s), 9.98 (1H, s)

30 (19) 3-Acetyl-1-(2-chlorobenzyl)-2-methylindole-6-carboxamide

mp : 272-276°C

NMR ($\text{DMSO}-d_6$, δ) : 2.63 (3H, s), 2.65 (3H, s), 5.61 (2H, s), 6.17 (1H, d, $J=8\text{Hz}$), 7.18 (1H, t, $J=8\text{Hz}$),
35 7.27 (1H, br s), 7.32 (1H, t, $J=8\text{Hz}$), 7.57 (1H, d, $J=8\text{Hz}$), 7.80 (1H, d, $J=8\text{Hz}$), 7.94 (1H, br s), 8.03

- 172 -

(1H, s), 8.11 (1H, s)

(20) 1-(2-Chlorobenzyl)-2-methyl-3-propionylindole-6-carboxamide

5 mp : 215-217°C

NMR (DMSO-d₆, δ) : 1.14 (3H, t, J=7Hz), 2.64 (3H, s),
3.04 (2H, q, J=7Hz), 5.62 (2H, s), 6.18 (1H, d,
J=8Hz), 7.18 (1H, t, J=8Hz), 7.29 (1H, br s), 7.32
(1H, t, J=8Hz), 7.57 (1H, d, J=8Hz), 7.79 (1H, d,
10 J=8Hz), 8.02 (1H, s), 8.10 (1H, d, J=8Hz)

(21) 1-(2-Chlorobenzo[b]thiophen-3-ylmethyl)-3-isobutyryl-2-methylindole-6-carboxamide

mp : 255°C (dec.)

15 NMR (DMSO-d₆, δ) : 1.13 (6H, d, J=7Hz), 2.63 (3H, s),
3.47 (1H, m), 5.84 (2H, s), 7.2-7.42 (4H, m), 7.48
(1H, d, J=8Hz), 7.89 (1H, br s), 7.95-8.0 (2H, m),
8.23 (1H, s)

20 (22) 1-(Benzothiazol-2-ylmethyl)-2-ethyl-3-isobutyrylindole-6-carboxamide

mp : 188-190.5°C (dec.)

NMR (CDCl₃, δ) : 1.28 (3H, t, J=7Hz), 1.29 (6H, d,
J=7Hz), 3.27 (2H, q, J=7Hz), 3.53 (1H, m), 5.82
25 (2H, s), 7.36 (1H, t, J=8Hz), 7.49 (1H, t, J=8Hz),
7.66 (1H, d, J=8Hz), 7.74 (1H, d, J=8Hz), 7.97 (1H,
d, J=8Hz), 8.02 (1H, d, J=8Hz), 8.07 (1H, s)

30 (23) 1-(Benzo[b]thiophen-5-ylmethyl)-3-isobutyryl-2-propylindole-6-carboxamide

mp : 189-192°C (dec.)

NMR (CDCl₃, δ) : 1.02 (3H, t, J=7Hz), 1.31 (6H, d,
J=7Hz), 1.62 (2H, m), 3.14 (2H, m), 3.57 (1H, m),
5.58 (2H, s), 7.02 (1H, d, J=8Hz), 7.18 (1H, d,
35 J=6Hz), 7.29 (1H, s), 7.43 (1H, d, J=6Hz), 7.60

- 173 -

(1H, d, J=8Hz), 7.79 (1H, d, J=8Hz), 7.92 (1H, s),
7.97 (1H, d, J=8Hz)

5 (24) 1-(2,4-Dichlorobenzyl)-3-isobutyryl-2-propylindole-6-
carboxamide

mp : 191-192°C

10 NMR (DMSO-d₆, δ) : 0.92 (3H, t, J=7Hz), 1.18 (6H, d,
J=7Hz), 1.45 (2H, sextet, J=7Hz), 3.00-3.05 (2H,
m), 3.55 (2H, septet, J=7Hz), 5.60 (2H, s), 6.18
(1H, d, J=8Hz), 7.28 (1H, dd, J=2, 8Hz), 7.31 (1H,
s), 7.76 (1H, d, J=2Hz), 7.82 (1H, d, J=8Hz), 7.92
(1H, br s), 7.94 (1H, s), 7.98 (1H, d, J=8Hz)

15 (25) 3-Isobutyryl-2-propyl-1-(3-pyridylmethyl)indole-6-
carboxamide

mp : 230-235°C

20 NMR (CDCl₃, δ) : 1.02 (3H, t, J=7Hz), 1.30 (6H, d,
J=7Hz), 1.60 (2H, sextet, J=7Hz), 3.08-3.16 (2H,
m), 3.56 (2H, septet, J=7Hz), 5.48 (2H, s), 7.19-
7.24 (2H, m), 7.61 (1H, d, J=8Hz), 7.92 (1H, s),
7.96 (1H, d, J=8Hz), 8.38 (1H, d, J=2Hz), 8.52 (1H,
dd, J=2, 5Hz)

25 (26) 3-Isobutyryl-2-propyl-1-(1-naphthylmethyl)indole-6-
carboxamide

mp : 202-203°C

30 NMR (CDCl₃, δ) : 0.96 (3H, t, J=7Hz), 1.34 (6H, d,
J=7Hz), 1.61-1.68 (2H, m), 3.08 (2H, dd, J=7, 8Hz),
3.61 (1H, septet, J=7Hz), 5.90 (2H, s), 6.28 (1H,
d, J=8Hz), 7.21 (1H, t, J=8Hz), 7.58-7.69 (3H, m),
7.76 (1H, d, J=8Hz), 7.78 (1H, s), 7.94 (1H, d,
J=8Hz), 8.00 (1H, d, J=8Hz), 8.08 (1H, d, J=8Hz)

35 (27) 3-Isobutyryl-2-propyl-1-(2-naphthylmethyl)indole-6-
carboxamide

- 174 -

mp : 189-190°C

5 NMR (CDCl₃, δ) : 0.98 (3H, t, J=7Hz), 1.30 (6H, d, J=7Hz), 1.55-1.68 (2H, m), 3.14-3.18 (2H, m), 3.58 (1H, septet, J=7Hz), 5.58 (2H, s), 7.15 (1H, dd, J=1, 8Hz), 7.28 (1H, s), 7.42-7.48 (2H, m), 7.60-7.66 (2H, m), 7.78 (2H, d, J=8Hz), 7.93 (1H, d, J=1Hz), 7.98 (1H, d, J=8Hz)

(28) 1-Allyl-3-isobutyryl-2-propylindole-6-carboxamide

10 mp : 155-158°C

15 NMR (CDCl₃, δ) : 1.06 (3H, t, J=7Hz), 1.27 (6H, d, J=7Hz), 1.71 (2H, m), 3.11 (2H, m), 3.51 (1H, m), 4.83 (2H, m), 4.86 (1H, m), 5.19 (1H, m), 5.96 (1H, m), 7.58 (1H, d, J=8Hz), 7.89 (1H, d, J=8Hz), 7.96 (1H, s)

(29) 1-(2-Chlorobenzyl)-3-isobutyryl-2-(1-propenyl)indole-6-carboxamide

mp : 190-193°C

20 NMR (CDCl₃, δ) : 1.23 (6H, d, J=7Hz), 1.93 (3H, d, J=7Hz), 3.51 (1H, m), 5.48 (2H, s), 5.91 (1H, dq, J=15, 7Hz), 6.41 (1H, d, J=8Hz), 6.71 (1H, d, J=15Hz), 7.07 (1H, t, J=8Hz), 7.23 (1H, t, J=8Hz), 7.46 (1H, d, J=8Hz), 7.62 (1H, d, J=8Hz), 7.80 (1H, s), 8.24 (1H, d, J=8Hz)

25

(30) 1-(2-Chlorobenzyl)-2-(1-hydroxypropyl)-3-isobutyrylindole-6-carboxamide

mp : 220-223°C

30 NMR (CDCl₃, δ) : 0.94 (3H, t, J=7Hz), 1.32 (3H, d, J=7Hz), 1.39 (3H, d, J=7Hz), 1.52 (1H, m), 1.93 (1H, m), 3.69 (1H, m), 4.68 (1H, m), 5.48 (1H, d, J=17Hz), 5.66 (1H, d, J=17Hz), 6.33 (1H, d, J=10Hz), 6.43 (1H, d, J=8Hz), 7.07 (1H, t, J=8Hz), 7.21 (1H, t, J=8Hz), 7.44 (1H, d, J=8Hz), 7.68 (1H, s)

35

- 175 -

d, J=8Hz), 7.92 (1H, s), 7.96 (1H, d, J=8Hz)

(31) 1-(2-Chlorobenzyl)-3-(3,3-dimethylbutanoyl)indole-6-carboxamide

5 mp : 202-205°C

NMR (CDCl₃, δ) : 1.08 (9H, s), 2.69 (2H, s), 5.50 (2H, s), 6.73 (1H, d, J=8Hz), 7.14 (1H, t, J=8Hz), 7.28 (1H, t, J=8Hz), 7.45 (1H, d, J=8Hz), 7.62 (1H, d, J=8Hz), 7.80 (1H, s), 7.99 (1H, s), 8.53 (1H, d, J=8Hz)

10

(32) 1-(2-Chlorobenzyl)-2-propylindole-6-carboxamide

mp : 174-177°C

NMR (CDCl₃, δ) : 1.00 (3H, t, J=7Hz), 1.74 (2H, m), 2.61 (2H, t, J=7Hz), 5.43 (2H, s), 6.15 (1H, d, J=8Hz), 6.44 (1H, s), 7.00 (1H, t, J=8Hz), 7.18 (1H, t, J=8Hz), 7.4-7.5 (2H, m), 7.61 (1H, d, J=8Hz), 7.79 (1H, s)

15

20 (33) 1-(2-Bromobenzyl)-2-propylindole-6-carboxamide

mp : 166-168°C

NMR (CDCl₃, δ) : 1.00 (3H, t, J=7Hz), 1.73 (2H, m), 2.59 (2H, m), 5.36 (2H, s), 6.10 (1H, d, J=8Hz), 6.42 (1H, s), 7.0-7.15 (2H, m), 7.46 (1H, dd, J=1, 8Hz), 7.61 (1H, dd, J=1, 8Hz), 7.76 (1H, s)

25

(34) 2-Acetyl-1-(2-chlorobenzyl)-3-methylindole-6-carboxamide

mp : 234-236°C

NMR (DMSO-d₆, δ) : 2.58 (3H, s), 2.71 (3H, s), 5.79 (2H, s), 6.03 (1H, d, J=8Hz), 7.09 (1H, t, J=8Hz), 7.24 (1H, t, J=8Hz), 7.35 (1H, br s), 7.50 (1H, d, J=8Hz), 7.70 (1H, d, J=8Hz), 7.92 (1H, d, J=8Hz), 7.98 (1H, s), 7.99 (1H, br s)

30

35 (35) 2-Chloro-1-(2-chlorobenzyl)-3-ethylindole-6-carboxamide

- 176 -

mp : 195-198°C

5 NMR (CDCl₃, δ) : 1.27 (3H, t, J=7Hz), 2.83 (2H, q, J=7Hz), 5.49 (2H, s), 6.29 (1H, d, J=8Hz), 7.03 (1H, t, J=8Hz), 7.18 (1H, t, J=8Hz), 7.42 (1H, d, J=8Hz), 7.50 (1H, d, J=8Hz), 7.63 (1H, d, J=8Hz), 7.77 (1H, s)

(36) 1-(2-Chlorobenzyl)-2-propionyl-3-propylindole-6-carboxamide

10 mp : 165-167°C

15 NMR (CDCl₃, δ) : 1.05 (3H, t, J=7Hz), 1.13 (3H, t, J=7Hz), 1.76 (2H, m), 2.93 (2H, q, J=7Hz), 3.08 (2H, m), 5.70 (2H, s), 6.23 (1H, d, J=8Hz), 6.97 (1H, t, J=8Hz), 7.12 (1H, t, J=8Hz), 7.47 (1H, d, J=8Hz), 7.53 (1H, d, J=8Hz), 7.74 (1H, s), 7.76 (1H, d, J=8Hz)

(37) 1-(2-Chlorobenzyl)-2-isobutyryl-3-propylindole-6-carboxamide

20 mp : 159-160.5°C

25 NMR (CDCl₃, δ) : 1.03 (3H, t, J=7Hz), 1.12 (6H, d, J=7Hz), 1.76 (2H, m), 3.04 (2H, m), 3.36 (1H, m), 5.66 (2H, s), 6.29 (1H, d, J=8Hz), 6.99 (1H, t, J=8Hz), 7.14 (1H, t, J=8Hz), 7.38 (1H, d, J=8Hz), 7.56 (1H, d, J=8Hz), 7.76 (1H, d, J=8Hz), 7.77 (1H, s)

(38) 1-(2-Chlorobenzyl)-3-(3-oxo-1-butenyl)indole-6-carboxamide

30 mp : 248-250°C

35 NMR (DMSO-d₆, δ) : 2.30 (3H, s), 5.61 (2H, s), 6.74 (1H, d, J=8Hz), 6.75 (1H, d, J=15Hz), 7.2-7.4 (3H, m), 7.54 (1H, d, J=8Hz), 7.77 (1H, d, J=8Hz), 7.80 (1H, d, J=15Hz), 7.98 (1H, br s), 8.04 (1H, d, J=8Hz), 8.11 (1H, s), 8.14 (1H, s)

- 177 -

(39) 4-(2-Chlorobenzyl)-3-oxo-1,2,3,4-tetrahydrocyclopent[b]indole-6-carboxamide

mp : 289°C (dec.)

5 NMR (DMSO-d₆, δ) : 2.95 (2H, m), 3.10 (2H, m), 5.67 (2H, s), 6.37 (1H, d, J=8Hz), 7.16 (1H, t, J=8Hz), 7.28 (1H, t, J=8Hz), 7.40 (1H, br s), 7.53 (1H, d, J=8Hz), 7.74 (1H, d, J=8Hz), 7.88 (1H, d, J=8Hz), 8.01 (1H, br s), 8.07 (1H, s)

10 (40) 4-(6-Chloro-3,4-methylenedioxybenzyl)-3-oxo-1,2,3,4-tetrahydrocyclopent[b]indole-6-carboxamide

mp : 282°C (dec.)

15 NMR (DMSO-d₆, δ) : 2.98 (2H, m), 3.09 (2H, m), 5.54 (2H, s), 5.97 (2H, s), 5.98 (1H, s), 7.17 (1H, s), 7.43 (1H, br s), 7.71 (1H, d, J=8Hz), 7.86 (1H, d, J=8Hz), 8.03 (1H, br s), 8.05 (1H, s)

(41) 1-[2-Chloro-4-(N-phenylsulfonylcarbamoyl)benzyl]-3-isobutyryl-2-propylindole-6-carboxamide

20 mp : 147-150°C

25 NMR (DMSO-d₆, δ) : 0.88 (3H, t, J=7Hz), 1.18 (6H, d, J=7Hz), 1.45 (2H, sextet, J=7Hz), 2.98-3.03 (2H, m), 3.55 (1H, septet, J=7Hz), 5.68 (2H, s), 6.27 (1H, d, J=8Hz), 7.28 (1H, s), 7.60-7.64 (3H, m), 7.69 (1H, dd, J=2, 8Hz), 7.80 (1H, d, J=8Hz), 7.92-7.96 (4H, m), 8.06 (1H, s)

Example 76

30 The following compound described in (1) to (5) were prepared by a similar manner to that of Example 6.

(1) 1-(6-Chloro-3,4-methylenedioxybenzyl)-3-methoxyacetyl-2-propylindole-6-carboxamide

35 (2) 1-(2-Chlorobenzyl)-3-ethoxyacetyl-2-propylindole-6-

- 178 -

carboxamide

- 5 NMR (DMSO- d_6 , δ) : 0.93 (3H, t, J=7Hz), 1.18 (3H, t, J=7Hz), 1.46 (2H, sextet, J=7Hz), 3.03 (3H, t, J=7Hz), 3.62 (2H, q, J=7Hz), 4.74 (2H, s), 5.63 (2H, s), 6.22 (1H, d, J=8Hz), 7.17 (1H, t, J=8Hz), 7.30 (1H, s), 7.33 (1H, t, J=8Hz), 7.58 (1H, d, J=8Hz), 7.80 (1H, d, J=8Hz), 7.92 (1H, d, J=8Hz), 7.94 (1H, s), 8.00 (1H, s)
- 10 (3) 1-(2-Chlorobenzyl)-3-isobutyryl-2-propylindol-6-ylacetamide
mp : 146-148°C
IR (KBr) : 1715, 1650 cm^{-1}
15 NMR (CDCl₃, δ) : 1.01 (3H, t, J=7Hz), 1.30 (6H, d, J=7Hz), 1.57-1.67 (2H, m), 3.02-3.08 (2H, m), 3.51-3.60 (1H, m), 3.66 (2H, s), 5.45 (2H, s), 6.29 (1H, d, J=7.5Hz), 7.04-7.09 (2H, m), 7.21 (2H, t, J=7.5Hz), 7.47 (1H, d, J=7.5Hz), 7.93 (1H, d, J=7.5Hz)
- 20 MASS (m/z) : 411 (M^+ +1), 74 (bp)
- (4) 1-(6-Chloro-3,4-methylenedioxybenzyl)-3-isobutyryl-2-propylindole-6-ylacetamide
mp : 136-138°C
25 IR (KBr) : 1655, 1505 cm^{-1}
NMR (CDCl₃, δ) : 1.04 (3H, t, J=7Hz), 1.29 (6H, d, J=7Hz), 1.55-1.67 (2H, m), 3.01-3.07 (2H, m), 3.50-3.58 (1H, m), 3.69 (2H, s), 5.33 (2H, s), 5.75 (1H, s), 5.90 (2H, s), 6.92 (1H, s), 7.09 (1H, s), 7.19 (1H, d, J=7.5Hz), 7.91 (1H, d, J=7.5Hz)
30 MASS (m/z) : 455 (M^+ +1), 74 (bp)
- (5) 1-(2-Chlorobenzyl)-3-nitro-2-propylindole-6-carboxamide
35 NMR (DMSO- d_6 , δ) : 0.95 (3H, t, J=7Hz), 1.54 (2H, sextet, J=7Hz), 3.13-3.17 (2H, m), 5.72 (2H, s),

- 179 -

6.44 (1H, d, J=8Hz), 7.20 (1H, t, J=8Hz), 7.36 (1H, t, J=8Hz), 7.42 (1H, s), 7.60 (1H, d, J=8Hz), 7.96 (1H, d, J=8Hz), 8.03 (1H, s), 8.10 (1H, s), 8.22 (1H, d, J=8Hz)

5

Example 77

The following compounds described in (1) to (13) were prepared in a similar manner to that of Example 26.

- 10 (1) 1-(4-Chloro-2-fluorobenzyl)-3-methoxyacetyl-2-propylindole-6-carboxamide
mp : 192-193°C
NMR (DMSO-d₆, δ) : 0.94 (3H, t, J=7Hz), 1.44 (2H, sextet, J=7Hz), 3.09 (2H, t, J=7Hz), 3.41 (3H, s),
15 4.69 (2H, s), 5.64 (2H, s), 6.50 (1H, t, J=8Hz), 7.18 (1H, dd, J=2, 8Hz), 7.33 (1H, s), 7.55 (1H, dd, J=2, 8Hz), 7.79 (1H, d, J=8Hz), 7.89 (1H, d, J=8Hz), 7.92 (1H, s), 8.06 (1H, s)
- 20 (2) 1-(2,4-Dichlorobenzyl)-3-methoxyacetyl-2-propylindole-6-carboxamide
mp : 203-205°C
NMR (DMSO-d₆, δ) : 0.94 (3H, t, J=7Hz), 1.98 (2H, sextet, J=7Hz), 3.04 (2H, t, J=7Hz), 3.42 (3H, s),
25 4.71 (2H, s), 5.60 (2H, s), 6.20 (1H, d, J=8Hz), 7.27 (1H, dd, J=2, 8Hz), 7.32 (1H, s), 7.77 (1H, d, J=2Hz), 7.82 (1H, d, J=8Hz), 7.92 (1H, d, J=8Hz), 7.94 (1H, s), 7.98 (1H, s)
- 30 (3) 1-(4-Bromo-2-chlorobenzyl)-3-methoxyacetyl-2-propylindole-6-carboxamide
mp : 178-180°C
NMR (DMSO-d₆, δ) : 0.94 (3H, t, J=7Hz), 1.48 (2H, sextet, J=7Hz), 3.04 (2H, t, J=7Hz), 3.42 (3H, s),
35 4.68 (2H, s), 5.57 (2H, s), 6.13 (1H, d, J=8Hz),

- 180 -

7.30 (1H, s), 7.38 (1H, dd, J=2, 8Hz), 7.80 (1H, d, J=8Hz), 7.86 (1H, d, J=2Hz), 7.90 (1H, d, J=8Hz), 7.93 (1H, s), 7.97 (1H, s)

5 (4) 1-(4-Bromo-2-fluorobenzyl)-3-methoxyacetyl-2-propylindole-6-carboxamide

mp : 197-199°C

10 NMR (DMSO-d₆, δ) : 0.94 (3H, t, J=7Hz), 1.48 (2H, sextet, J=7Hz), 3.09 (2H, t, J=7Hz), 3.40 (3H, s), 4.67 (2H, s), 5.62 (2H, s), 6.43 (1H, d, J=8Hz), 7.28 (1H, dd, J=2, 8Hz), 7.65 (1H, dd, J=2, 8Hz), 7.78 (1H, d, J=8Hz), 7.90 (1H, d, J=8Hz), 7.92 (1H, s), 8.05 (1H, s)

15 (5) 1-(2-Chloro-4-fluorobenzyl)-3-methoxyacetyl-2-propylindole-6-carboxamide

mp : 174-176°C

20 NMR (DMSO-d₆, δ) : 0.93 (3H, t, J=7Hz), 1.48 (2H, sextet, J=7Hz), 3.04 (2H, t, J=7Hz), 3.42 (3H, s), 4.70 (2H, s), 5.58 (2H, s), 6.25 (1H, d, J=8Hz), 7.06 (1H, dt, J=2, 8Hz), 7.32 (1H, s), 7.50 (1H, dd, J=2, 8Hz), 7.80 (1H, d, J=8Hz), 7.92 (1H, d, J=8Hz), 7.94 (1H, s), 8.00 (1H, s)

25 (6) 1-(Benzo[b]thiophen-5-ylmethyl)-3-methoxyacetyl-2-propylindole-6-carboxamide

mp : 197-199°C (dec.)

30 NMR (DMSO-d₆, δ) : 0.92 (3H, t, J=7Hz), 1.48 (2H, sextet, J=7Hz), 3.14 (2H, t, J=7Hz), 3.42 (3H, s), 4.72 (2H, s), 5.74 (2H, s), 7.10 (1H, d, J=8Hz), 7.28 (1H, s), 7.38 (1H, d, J=5Hz), 7.44 (1H, s), 7.75 (1H, d, J=5Hz), 7.78 (1H, d, J=8Hz), 7.88 (1H, d, J=8Hz), 7.92 (1H, s), 7.96 (1H, d, J=8Hz), 8.12 (1H, s)

- 181 -

(7) Methyl 1-(2,4-dichlorobenzyl)-3-isobutyryl-2-propylindole-6-carboxylate

5 NMR (CDCl₃, δ) : 1.02 (3H, t, J=7Hz), 1.31 (6H, d, J=7Hz), 1.60 (2H, sextet, J=7Hz), 3.06 (2H, t, J=7Hz), 3.58 (2H, septet, J=7Hz), 3.93 (3H, s), 5.46 (2H, s), 6.16 (1H, d, J=8Hz), 7.04 (1H, d, J=8Hz), 7.50 (1H, s), 7.90 (1H, s), 7.96 (2H, s)

10 (8) Methyl 3-isobutyryl-2-propyl-1-(3-pyridylmethyl)indole-6-carboxylate

15 NMR (CDCl₃, δ) : 1.02 (3H, t, J=7Hz), 1.30 (6H, d, J=7Hz), 1.60 (2H, sextet, J=7Hz), 3.12 (2H, t, J=7Hz), 3.56 (2H, septet, J=7Hz), 3.92 (3H, s), 5.48 (2H, s), 7.14-7.23 (2H, m), 7.92-7.95 (2H, m), 7.98 (1H, s), 8.42 (1H, d, J=2Hz), 8.54 (1H, d, J=5Hz)

(9) Methyl 3-isobutyryl-2-propyl-1-(1-naphthylmethyl)indole-6-carboxylate

20 NMR (CDCl₃, δ) : 0.97 (3H, t, J=7Hz), 1.34 (6H, d, J=7Hz), 1.64 (2H, sextet, J=7Hz), 3.04-3.10 (2H, m), 3.63 (1H, septet, J=7Hz), 3.84 (3H, s), 5.92 (2H, s), 6.28 (1H, d, J=8Hz), 7.22 (1H, t, J=8Hz), 7.62 (1H, t, J=8Hz), 7.69 (1H, t, J=8Hz), 7.77 (1H, d, J=8Hz), 7.77 (2H, s), 7.92 (1H, s)

25

(10) Methyl 3-isobutyryl-2-propyl-1-(2-naphthylmethyl)indole-6-carboxylate

30 NMR (CDCl₃, δ) : 1.00 (3H, t, J=7Hz), 1.32 (6H, d, J=7Hz), 1.55-1.68 (2H, m), 3.13-3.18 (2H, m), 3.60 (1H, septet, J=7Hz), 3.88 (3H, s), 5.62 (2H, s), 7.17 (1H, d, J=8Hz), 7.29 (2H, s), 7.42-7.48 (2H, m), 7.64-7.68 (1H, m), 7.80 (2H, d, J=2Hz), 7.96 (2H, s), 8.04 (1H, s)

35

- 182 -

(11) Methyl 1-(6-chloro-3,4-methylenedioxybenzyl)-3-methoxyacetyl-2-propylindole-6-carboxylate

5 NMR (CDCl₃, δ) : 1.04 (3H, t, J=7Hz), 1.56-1.72 (2H, m), 3.06-3.13 (2H, m), 3.58 (3H, s), 3.93 (3H, s), 4.73 (2H, s), 5.40 (2H, s), 5.70 (1H, s), 5.88 (2H, s), 6.92 (1H, s), 7.83 (1H, d, J=8Hz), 7.96 (1H, s), 7.98 (1H, d, J=8Hz)

10 (12) Methyl 1-(2-chlorobenzyl)-3-ethoxyacetyl-2-propylindole-6-carboxylate

15 NMR (CDCl₃, δ) : 1.03 (3H, t, J=7Hz), 1.34 (3H, t, J=7Hz), 1.56-1.70 (2H, m), 3.10 (3H, t, J=7Hz), 3.77 (2H, q, J=7Hz), 3.92 (3H, s), 4.79 (2H, s), 5.52 (2H, s), 6.24 (1H, d, J=8Hz), 7.03 (1H, t, J=8Hz), 7.22 (1H, t, J=8Hz), 7.46 (1H, d, J=8Hz), 7.85 (1H, d, J=8Hz), 7.92 (1H, s), 7.98 (1H, d, J=8Hz)

20 (13) 1-(2-Chloro-4-methoxycarbonylbenzyl)-3-isobutyryl-2-propylindole-6-carboxamide

25 NMR (CDCl₃, δ) : 1.01 (3H, t, J=7Hz), 1.32 (6H, d, J=7Hz), 1.60 (2H, sextet, J=7Hz), 3.02-3.06 (2H, m), 3.56 (1H, septet, J=7Hz), 3.90 (3H, s), 5.53 (2H, s), 6.28 (1H, d, J=8Hz), 7.63 (1H, d, J=8Hz), 7.69 (1H, d, J=8Hz), 7.82 (1H, s), 7.98 (1H, d, J=8Hz), 8.14 (1H, s)

30

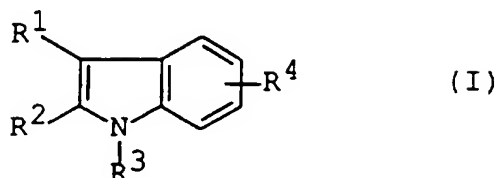
35

- 183 -

C L A I M S

What we claim is :

1. A compound of the formula :



wherein

- R^1 is hydrogen, halogen, nitro, carboxy, protected carboxy, acyl, cyano, hydroxyimino(lower)alkyl, lower alkenyl optionally substituted with oxo, or lower alkyl optionally substituted with protected carboxy, carboxy or hydroxy;
- R^2 is hydrogen, halogen, lower alkenyl, acyl, or lower alkyl optionally substituted with protected carboxy, carboxy, lower alkoxy or hydroxy;
- R^3 is lower alkenyl or lower alkyl, both of which are optionally substituted with one or more substituent(s) selected from the group consisting of
- (1) oxo,
 - (2) aryl optionally substituted with one or more substituent(s) selected from the group consisting of halogen, aryl, lower alkoxy, lower alkylenedioxy, cyano, nitro, carboxy, protected carboxy, acyl, and amino optionally substituted with acyl or protected carboxy, and
 - (3) a heterocyclic group optionally substituted

- 184 -

with halogen; and

R⁴ is carboxy, protected carboxy, acyl, cyano, halogen, a heterocyclic group, amino optionally substituted with acyl or protected carboxy, or lower alkyl optionally substituted with protected carboxy, carboxy or acyl;

in addition to their significances above,

R¹ and R², together with the carbon atoms to which they are attached, represent a 4- to 7-membered carbocyclic ring optionally substituted with oxo,

or its pharmaceutically acceptable salt.

2. A compound of claim 1, wherein

R¹ is cyano, acyl, or lower alkyl optionally substituted with hydroxy,

R² is hydrogen, acyl, lower alkenyl, or lower alkyl optionally substituted with lower alkoxy or hydroxy,

R³ is methyl substituted with aryl or a heterocyclic group, wherein aryl is optionally substituted with one or more substituent(s) selected from the group consisting of halogen, lower alkylendioxy, protected carboxy and carboxy, and

R⁴ is acyl, cyano, or a heterocyclic group,

in addition to their significances above,

R¹ and R², together with the carbon atoms to which they are attached, represent a 4- to 7-membered carbocyclic ring optionally substituted with oxo.

3. A compound of claim 2, wherein

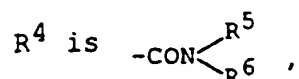
R¹ is lower alkyl, or lower alkanoyl optionally substituted with hydroxy, lower alkoxy or aryl,

R² is hydrogen, lower alkenyl, or lower alkyl optionally

- 185 -

substituted with lower alkoxy, and
 R^3 is benzyl optionally substituted with one or more
 substituent(s) selected from the group consisting
 of halogen and lower alkylenedioxy.

4. A compound of claim 3, wherein



R^5 is hydrogen, or lower alkyl, and
 R^6 is hydrogen, hydroxy, lower alkoxy, arylsulfonyl,
 a heterocyclic group, or lower alkyl optionally
 substituted with lower cycloalkyl or a heterocyclic
 group,

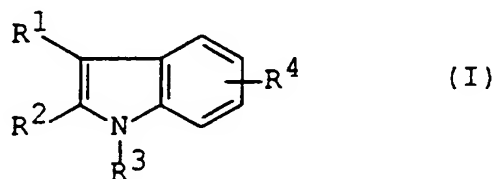
in addition to their significances above,

R^5 and R^6 , together with the nitrogen atom to
 which they are attached, may represent a
 heterocyclic group.

5. A compound of claim 4, wherein

R^1 is lower alkanoyl optionally substituted with alkoxy,
 R^2 is lower alkyl, and
 R^4 is carbamoyl.

6. A process for preparing a compound of the formula :



wherein

R^1 is hydrogen, halogen, nitro, carboxy, protected

- 186 -

carboxy, acyl, cyano, hydroxyimino(lower)alkyl, lower alkenyl optionally substituted with oxo, or lower alkyl optionally substituted with protected carboxy, carboxy or hydroxy;

R^2 is hydrogen, halogen, lower alkenyl, acyl, or lower alkyl optionally substituted with protected carboxy, carboxy, lower alkoxy or hydroxy;

R^3 is lower alkenyl or lower alkyl, both of which are optionally substituted with one or more substituent(s) selected from the group consisting of

- (1) oxo,
- (2) aryl optionally substituted with one or more substituent(s) selected from the group consisting of halogen, aryl, lower alkoxy, lower alkylenedioxy, cyano, nitro, carboxy, protected carboxy, acyl, and amino optionally substituted with acyl or protected carboxy, and
- (3) a heterocyclic group optionally substituted with halogen; and

R^4 is carboxy, protected carboxy, acyl, cyano, halogen, a heterocyclic group, amino optionally substituted with acyl or protected carboxy, or lower alkyl optionally substituted with protected carboxy, carboxy or acyl;

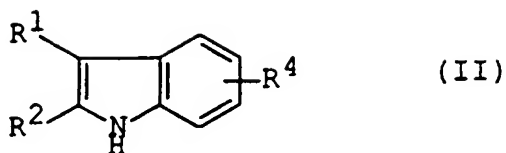
in addition to their significances above,

R^1 and R^2 , together with the carbon atoms to which they are attached, represent a 4- to 7-membered carbocyclic ring optionally substituted with oxo,

or its pharmaceutically acceptable salt, which comprises,

a) reacting a compound of the formula :

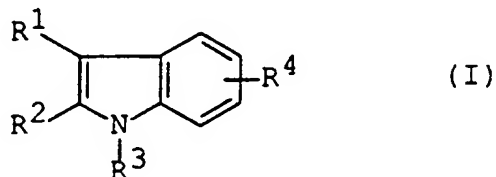
- 187 -



wherein R^1 , R^2 and R^4 are each as defined above,
or its salt, with a compound of the formula :

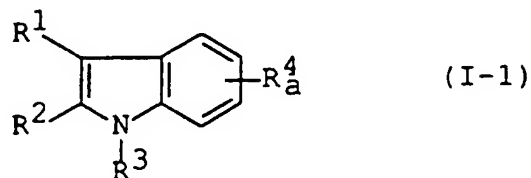


wherein R^3 is the one as defined above, and
 X^1 is a leaving group,
to give a compound of the formula :



wherein R^1 , R^2 , R^3 and R^4 are each as defined above,
or its salt ;

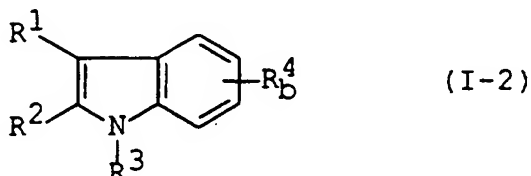
ii) subjecting a compound of the formula :



wherein R^1 , R^2 and R^3 are each as defined above, and

- 188 -

R_a^4 is protected carboxy or lower alkyl
substituted with protected carboxy,
or its salt,
to deesterification to give a compound of the formula :



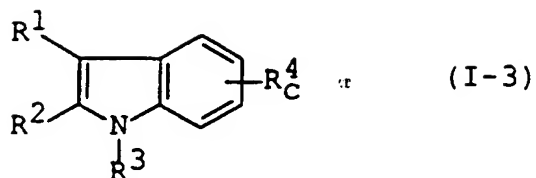
wherein R^1 , R^2 and R^3 are each as defined above, and
 R_b^4 is carboxy or lower alkyl substituted with
carboxy,
or its salt,

iii) reacting a compound of the formula (I-2) defined above,
or its reactive derivative at the carboxy group,
or its salt, with a compound of the formula :



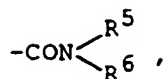
wherein R^5 is hydrogen or lower alkyl, and
 R^6 is hydrogen, hydroxy, lower alkoxy,
arylsulfonyl, a heterocyclic group, or
lower alkyl optionally substituted with
lower cycloalkyl or a heterocyclic group,
in addition to their significances above,
 R^5 and R^6 , together with the nitrogen atom to
which they are attached, may represent a
heterocyclic group,
or its reactive derivative at the amino group, or
its salt, to give a compound of the formula :

- 189 -



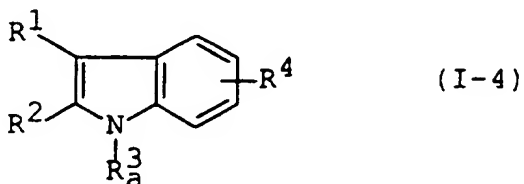
wherein R^1 , R^2 , R^3 , R^5 and R^6 are each as defined above,
and

R_C^4 is $-\text{CON} \begin{smallmatrix} \nearrow R^5 \\ \searrow R^6 \end{smallmatrix}$ or lower alkyl substituted with



or its salt;

iv) subjecting a compound of the formula :



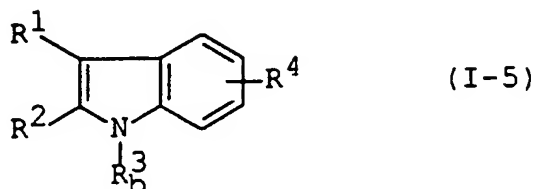
wherein R^1 , R^2 and R^4 are each as defined above, and
 R_a^3 is lower alkenyl or lower alkyl, both of
which are optionally substituted with oxo
and both of which are substituted with
aryl which is substituted with protected

- 190 -

carboxy,

or its salt,

to deesterification to give a compound of the formula :



wherein R^1 , R^2 and R^4 are each as defined above, and

R_D^3 is lower alkenyl or lower alkyl, both of

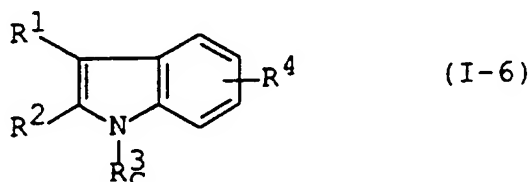
which are optionally substituted with oxo

and both of which are substituted with

aryl which is substituted with carboxy,

or its salt;

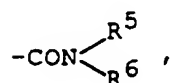
- v) reacting a compound of the formula (I-5) defined above, or its reactive derivative at the carboxy group, or its salt, with the compound of the formula (IV) defined above, or its reactive derivative at the amino group, or its salt, to give a compound of the formula :



- 191 -

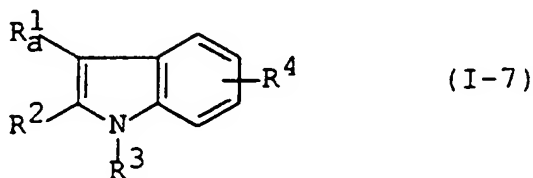
wherein R^1 , R^2 , R^3 , R^5 and R^6 are each as defined above,
and

R_C^3 is lower alkenyl or lower alkyl, both of
which are optionally substituted with oxo
and both of which are substituted with
aryl which is substituted with



or its salt;

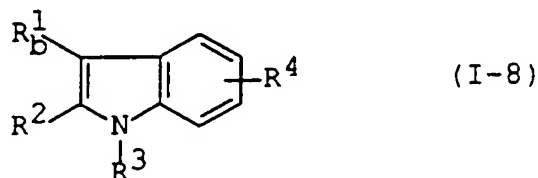
vi) reducing a compound of the formula :



wherein R^2 , R^3 and R^4 are each as defined above, and
 R_a^1 is lower alkanoyl optionally substituted with
protected carboxy or carboxy,

or its salt,

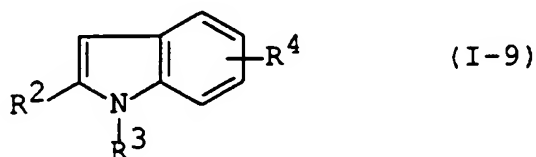
to give a compound of the formula :



- 192 -

wherein R^2 , R^3 and R^4 are each as defined above, and
 R_D^1 is lower alkyl optionally substituted with
 protected carboxy or carboxy,
 or its salt;

vii) reacting a compound of the formula :



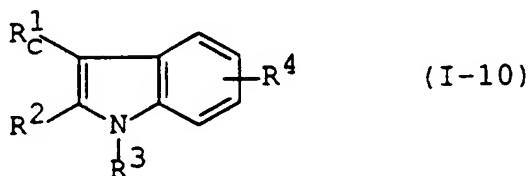
wherein R^2 , R^3 and R^4 are each as defined above,
 or its salt, with a compound of the formula :



wherein R_C^1 is lower alkanoyl, aroyl, or lower alkanoyl
 optionally substituted with protected
 carboxy, carboxy, or aryl,

X^2 is a leaving group,

or its salt, to give a compound of the formula :

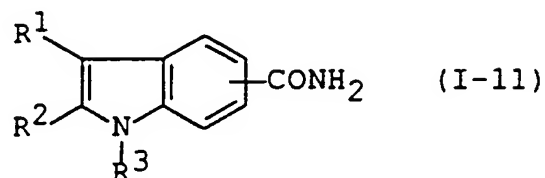


wherein R_C^1 , R^2 , R^3 and R^4 are each as defined above,

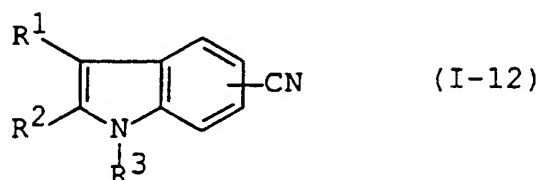
- 193 -

or its salt;

viii) dehydrating a compound of the formula :

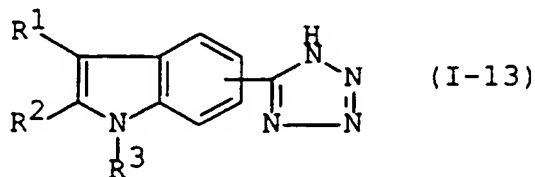


wherein R^1 , R^2 and R^3 are each as defined above,
or its salt, to give a compound of the formula :



wherein R^1 , R^2 and R^3 are each as defined above,
or its salt;

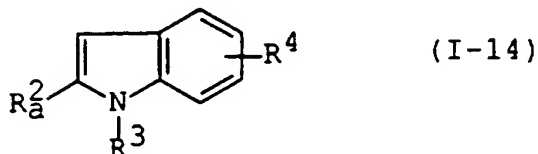
ix) reacting a compound of the formula (I-12) defined above,
or its salt, with azide compound, to give a compound of
the formula :



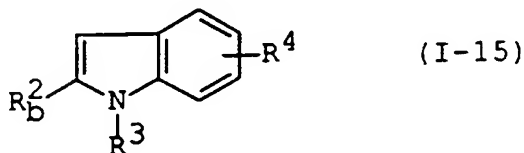
- 194 -

wherein R^1 , R^2 and R^3 are each as defined above,
or its salt;

x) subjecting a compound of the formula :



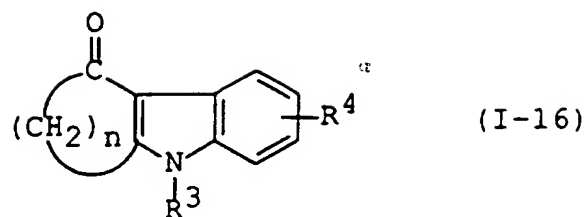
wherein R^3 and R^4 are each as defined above, and
 R_a^2 is lower alkyl substituted with protected
carboxy,
or its salt, to deesterification to give a compound of
the formula :



wherein R^3 and R^4 are each as defined above, and
 R_b^2 is lower alkyl substituted with carboxy,
or its salt;

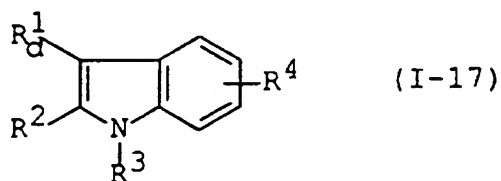
xi) subjecting a compound of the formula (I-15) defined
above, or its salt, to intramolecular acylation to give
a compound of the formula :

- 195 -

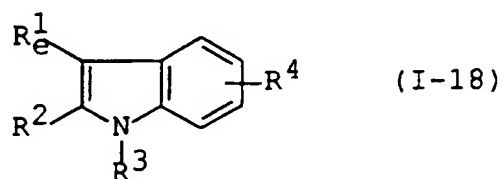


wherein R^3 and R^4 are each as defined above, and
 n is 1, 2, 3 or 4,
 or its salt;

xii) reacting a compound of the formula :

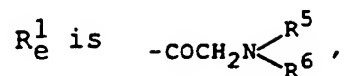


wherein R^2 , R^3 and R^4 are each as defined above, and
 R^1 is chloroacetyl,
 or its salt, with a compound of the formula (IV) defined
 above, or its salt, to give a compound of the formula :



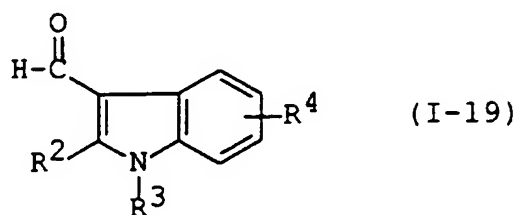
- 196 -

wherein R^2 , R^3 and R^4 are defined above, and



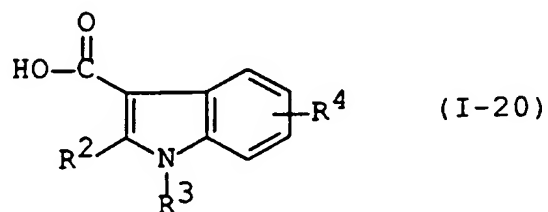
or its salt;

xiii) formylating a compound of the formula (I-9) defined above, or its salt, to give a compound of the formula :



wherein R^2 , R^3 and R^4 are each as defined above,
or its salt;

xiv) oxidizing a compound of the formula (I-19) defined above, or its salt, to give a compound of the formula :

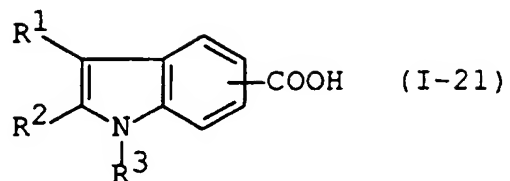


wherein R^2 , R^3 and R^4 are each as defined above,

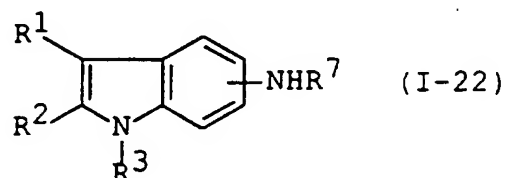
- 197 -

or its salt;

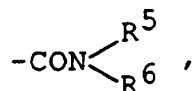
xv) subjecting a compound of the formula :



wherein R^1 , R^2 and R^3 are each as defined above,
or its salt, to rearrangement reaction to give a
compound of the formula :



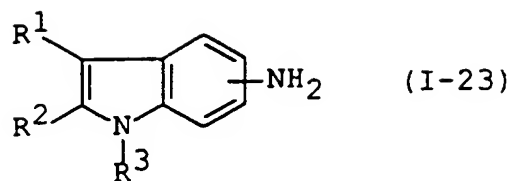
wherein R^1 , R^2 , R^3 , R^5 and R^6 are each as defined above,
and
 R^7 is hydrogen, protected carboxy, or



or its salt;

xvi) reacting a compound of the formula :

- 198 -



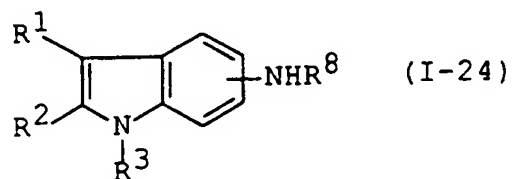
wherein R^1 , R^2 and R^3 are each as defined above,
 or its reactive derivative at the amino group,
 or its salt, with a compound of the formula :



wherein R^8 is acyl, and
 X^3 is leaving group,
 or its salt, or a compound of the formula :



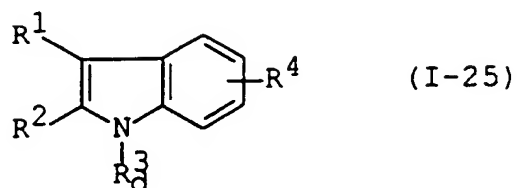
wherein R^9 is lower alkyl,
 to give a compound of the formula :



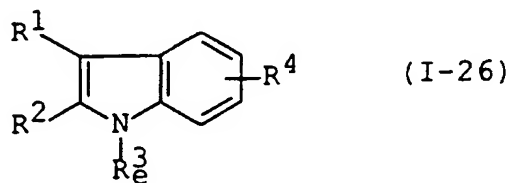
- 199 -

wherein R^1 , R^2 , R^3 and R^8 are same as defined above,
or its salt,

xvii) reducing a compound of the formula :



wherein R^1 , R^2 and R^4 are each as defined above, and
 R_d^3 is lower alkenyl or lower alkyl, both of
which are optionally substituted with oxo
and both of which are substituted with
aryl which is substituted with nitro,
or its salt, to give a compound of the formula :

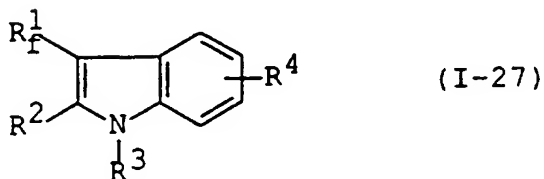


wherein R^1 , R^2 and R^4 are each as defined above, and
 R_e^3 is lower alkenyl or lower alkyl, both of
which are optionally substituted with oxo

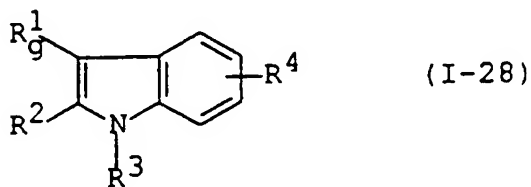
- 200 -

and both of which are substituted with
aryl which is substituted with amino,
or its salt;

xviii) subjecting a compound of the formula :



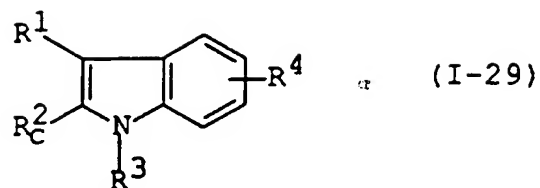
wherein R^2 , R^3 and R^4 are each as defined above, and
 R^1_F is lower alkanoyl substituted with lower
alkoxy,
or its salt, to dealkylation to give a compound of the
formula :



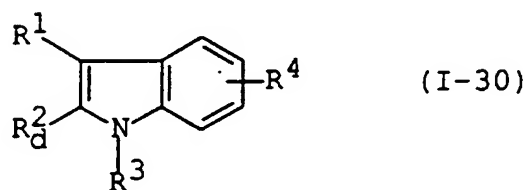
wherein R^2 , R^3 and R^4 are each as defined above, and
 R^1_G is lower alkanoyl substituted with hydroxy,
or its salt;

xix) oxidizing a compound of the formula :

- 201 -

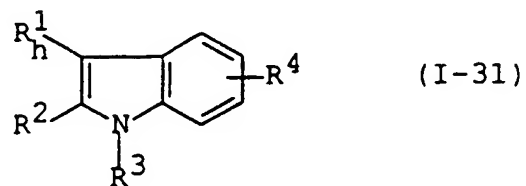


wherein R^1 , R^3 and R^4 are each as defined above, and
 R_C^2 is 1-hydroxy(lower)alkyl,
 or its salt, to give a compound of the formula :



wherein R^1 , R^3 and R^4 are each as defined above, and
 R_d^2 is lower alkanoyl,
 or its salt;

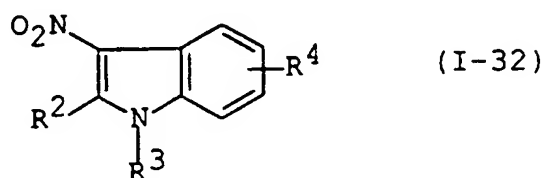
xx) halogenating a compound of the formula (I-9) defined
 above, or its salt, to give a compound of the formula :



- 202 -

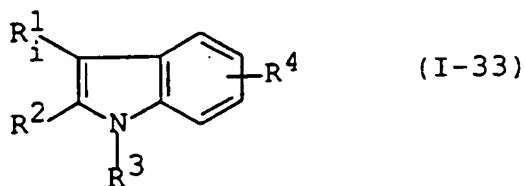
wherein R^2 , R^3 and R^4 are each as defined above, and
 R_H^1 is halogen,
 or its salt;

xxi) subjecting a compound of the formula (I-9) defined above, or its salt, to nitration to give a compound of the formula :



wherein R^2 , R^3 and R^4 are each as defined above,
 or its salt;

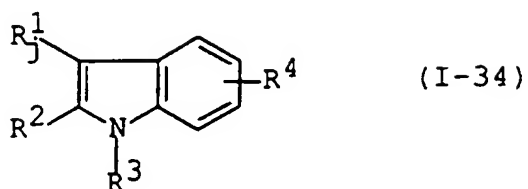
xxii) reducing a compound of the formula (I-7) defined above, or its salt, to give a compound of the formula :



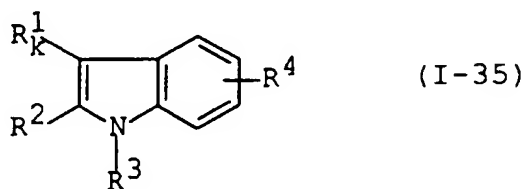
wherein R^2 , R^3 and R^4 are each as defined above, and
 R_1^1 is lower alkyl optionally substituted with
 protected carboxy or carboxy,
 or its salt;

- 203 -

xxiii) reacting a compound of the formula :



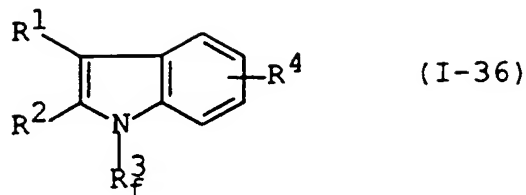
wherein R^2 , R^3 and R^4 are each as defined above, and
 R_j^1 is lower alkanoyl,
 or its salt, with hydroxylamine or its salt,
 to give a compound of the formula :



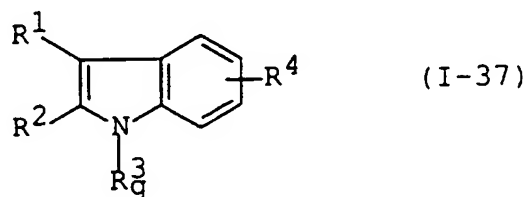
wherein R^2 , R^3 and R^4 are each as defined above, and
 R_k^1 is hydroxyimino(lower)alkyl,
 or its salt; or

xxiv) reacting a compound of the formula :

- 204 -



wherein R^1 , R^2 and R^4 are each as defined above,
 R^3 is lower alkenyl or lower alkyl, both of
 which are optionally substituted with oxo
 and both of which are substituted with
 aryl which is substituted with amino,
 or its reactive derivative at the amino group, or its
 salt, with a compound of the formula (VI) defined above
 or its salt, or a compound of the formula (VII) defined
 above, to give a compound of the formula :



wherein R^1 , R^2 and R^4 are each as defined above, and
 R^3 is lower alkenyl or lower alkyl, both of
 which are optionally substituted with oxo
 and both of which are substituted with
 aryl which is substituted with amino
 substituted with acyl,

- 205 -

or its salt.

- 5 7. A pharmaceutical composition comprising the compound of claim 1, as an active ingredient, in association with a pharmaceutically acceptable, substantially non-toxic carrier or excipient.
8. A compound of claim 1 for use as a medicament.
- 10 9. A use of the compound of claim 1 for the manufacture of a medicament for inhibiting cGMP-PDE.
- 15 10. A use of the compound of claim 1 for the manufacture of a medicament for treating or preventing angina, hypertension, pulmonary hypertension, congestive heart failure, glomerular diseases, renal tuburo-intestinal diseases, renal failure, atherosclerosis, conditions of reduced blood vessel patency, peripheral vascular disease, stroke, bronchitis, chronic asthma, allergic
20 asthma, allergic rhinitis, urticaria, impotence, diabetic complication, glaucoma or diseases characterized by disorders of gut motility.
- 25 11. A method for treating or preventing angina, hypertension, pulmonary hypertension, congestive heart failure, glomerular diseases, renal tuburo-intestinal diseases, renal failure, atherosclerosis, conditions of reduced blood vessel patency, peripheral vascular disease, stroke, bronchitis, chronic asthma, allergic
30 asthma, allergic rhinitis, urticaria, impotence, diabetic complication, glaucoma or diseases characterized by disorders of gut motility, by administering the compound of claim 1.
- 35 12. The use of a cyclic nucleotide-PDE inhibitors, or its

- 206 -

pharmaceutical acceptable salt, for preventing or treating glomerular diseases, renal tubulo-interstitial diseases, chronic renal failure or diabetic complications.

5

13. The use of a cyclic nucleotide-PDE inhibitors, or its pharmaceutical acceptable salt, for manufacturing a medicament for preventing or treating glomerular diseases, renal tubulo-interstitial diseases, chronic renal failure or diabetic complications.

10

15

20

25

30

35

INTERNATIONAL SEARCH REPORT

International Application No.
PCT/JP 96/00892

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D209/12 A61K31/40 C07D401/12 C07D403/12 C07D409/06
C07D405/06 C07D401/06 C07D403/04 C07D417/06 C07D209/42
C07D209/30 C07D209/88 C07D209/70

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CHEMICAL ABSTRACTS, vol. 120, no. 15, 11 April 1994 Columbus, Ohio, US; abstract no. 191719v, OKU, TERUO ET AL.: "Preparation of benzylbenzimidazoles as c-GMP phosphodiesterase inhibitors" XP002003189 see abstract & JP, A, 93 222 000 (FUJISAWA PHARMACEUTICAL CO., LTD.) --- -/--	1,9

☒ Further documents are listed in the continuation of box C.

☐ Patent family members are listed in annex.

* Special categories of cited documents:

- * "A" document defining the general state of the art which is not considered to be of particular relevance
- * "E" earlier document but published on or after the international filing date
- * "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- * "O" document referring to an oral disclosure, use, exhibition or other means
- * "P" document published prior to the international filing date but later than the priority date claimed

* "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

* "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

* "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

* "A" document member of the same patent family

Date of the actual completion of the international search

15 May 1996

Date of mailing of the international search report

29.05.96

Name and mailing address of the ISA
European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+ 31-70) 340-3016

Authorized officer

Van Bijlen, H

INTERNATIONAL SEARCH REPORT

International Application No
PCT/JP 96/00892

C(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>CHEMICAL ABSTRACTS, vol. 121, no. 1, 4 July 1994 Columbus, Ohio, US; abstract no. 7425t, "Inhibitors for c-GMP phosphodiesterase manufacture with Streptomyces." XP002003190 see abstract & JP,A,93 301 857 (FUJISAWA PHARMACEUTICAL CO.,LTD.) -----</p>	1,9

INTERNATIONAL SEARCH REPORT

I national application No.

PCT/JP 96/00892

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Please see attached sheet ./.
Claims not searched: 1-5, 11

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/SAJ

The vast number of theoretically conceivable compounds encompassed by the general formula (I) of claim 1 precludes a comprehensive documentary search as well as an on-line search in a structure data base and would not be economically justified (cf. Arts. 6, 15 and Rule 33 PCT; see Guidelines B III 1,1).